Standard Operating Procedure for Processing and Reporting Serious Adverse Events, Serious Adverse Device Effects and Unexpected Serious Adverse Device Effects for Medical Device Studies sponsored by University Hospitals of Leicester NHS Trust (UHL)

PGC Reference No: – C71/2017

OFFICE BASE

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1. Introduction

This Standard Operating Procedure (SOP) describes the process required by the University Hospitals of Leicester NHS Trust (UHL) for identifying, documenting and reporting all adverse events for medical device studies sponsored by Trust, in order to comply with the medical device regulations 2002, ISO 14155:2011 (Clinical investigations of medical devices for human subjects-Good Clinical Practice).

Researchers should be aware of the different definitions related to adverse events in medical device studies and the requirements with regards to the recording, reporting and review processes. Adverse events relating to trials involving medical devices can be classified into different categories. Further information on these categories is provided in Section 4:

- Adverse Event (AE)
- Adverse Device Effect (ADE)
- Serious Adverse Device Effect (SADE)
- Serious Adverse Event (SAE)
- Anticipated Serious Adverse Device Effect (ASADE)
- Unanticipated Serious Adverse Device Effect (USADE)

Investigator assessment of causality and expectedness is of particular importance. Safety reporting for medical device studies commences at the time of enrolment to the study. This is defined as the date a subject signs and dates the informed consent form.

The outcome is that the UHL fulfills the requirements as Sponsor to identify, document and report all categories of Adverse Events and Device Effects.

2. Scope

This SOP applies to all staff and external individuals involved in research activity involving CE Marked Devices utilised within their intended purpose, Proof of Concept studies and Clinical Investigation of non-CE marked devices or CE marked devices that are being used outside their intended use(s).

3. Definitions

Medical Device

Any health care product which is used for a patient in the diagnosis, treatment, prevention or alleviation of illness or injury.

“Medical device” means an instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any software necessary for its proper application which is:
a) Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of

- diagnosis, prevention, monitoring, treatment or alleviation of disease
- diagnosis, monitoring treatment, alleviation of, or compensation for, an injury
- investigation, replacement, modification, or support of the anatomy or of a physiological process
- supporting or sustaining life
- control of contraception
- disinfection of medical devices

b) Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means.

This definition of medical device is as per ISO 14155 Clinical investigation of medical devices for human subjects - Good Clinical Practice and does not apply to in vitro diagnostic medical devices (ISO 13485:2003).

CE Marked device studies
Post marketing studies where the product is used within its intended purpose.

Proof of Concept studies
Devices manufactured in-house in a healthcare establishment, are usually produced as a one-off model or in small numbers to determine proof of concept. Provided such devices are used within the same legal entity and on patients of that Trust, then the device(s) are not subject to the provisions of the Medical Devices Regulation.

Investigational Medical Device
An investigational medical device is a medical device being assessed for safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

Clinical Investigation Plan (CIP)
A document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record keeping of the clinical Investigation.

Investigator’s Brochure (IB)
A compilation of the current clinical and non-clinical information on the investigational medicinal device relevant to the clinical investigation.

Device Deficiency
Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.
Device Malfunction
Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan.

Adverse Event (AE)
An adverse event is an 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.

An adverse event can therefore be any unfavourable and unintended sign or abnormal laboratory results, symptom or disease temporarily associated with the use of the medical device/intervention, whether or not considered to be related to the medical device/intervention.

Adverse Device Effect (ADE)
An ADE is an adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

An ADE includes any event that is a result of use error or intentional misuse. Use error refers to an act or omission of an act that results in a different device response than intended by the manufacturer or expected by the user. An unexpected physiological response of the subject does not in itself constitute a use error.

Serious Adverse Device Effect (SADE)
A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. This includes device deficiencies that might have led to a serious adverse event if:
- Suitable action had not been taken or
- Intervention has not been made or
- If circumstances had been less fortunate

Serious Adverse Event (SAE)
In medical device research a serious adverse event is defined by ISO14155:2011 guidelines for medical device trials as untoward occurrence in a trial subject that:
- Results in death
- Is life threatening (the subject was at risk of death at the time of event)
- Requires hospitalisation or prolongation of an existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other serious Important Medical Event - an event that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed above should be considered.

A planned hospitalisation for a pre-existing condition, or procedure required by the Clinical Investigation Plan (CIP) without a serious deterioration in health is not considered to be a serious adverse event.
Anticipated Serious Adverse Device effect (ASADE)
A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the current version of the Risk Analysis Report or the Investigator's Brochure.

Unanticipated Serious Adverse Device Effect (USADE)
A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or Investigator's Brochure.

4. Adverse Event Categorisation
The relationship between the investigational medical device and the occurrence of each adverse event must be assessed and categorised by the Chief Investigator (CI) / Principal Investigator (PI) or the Sponsor agreed delegated medically qualified individual, utilising the device event categorisation flow chart (Appendix 1).

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Non Device Related</th>
<th>Device or Procedure Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-serious</td>
<td>Adverse Event (AE)</td>
<td>Adverse Device Effect (ADE)</td>
</tr>
<tr>
<td>Serious</td>
<td>Serious Adverse Event (SAE)</td>
<td>Serious Adverse Device Effect (SADE)</td>
</tr>
<tr>
<td></td>
<td>Anticipated</td>
<td>Unanticipated</td>
</tr>
<tr>
<td></td>
<td>Anticipated Serious Device Effect (ASADE)</td>
<td>Unanticipated Serious Device Effect (USADE)</td>
</tr>
</tbody>
</table>

5. Causality
The relationship between the investigational medical device and the occurrence of each adverse event will be assessed and categorised. The investigator will use clinical judgement to determine relationship. The investigator must consult the current version of the Risk Analysis Report and/or the Investigator’s Brochure where available.

Causality assessment
Any causality assessments must be made by the CI/PI or the Sponsor agreed delegated medically qualified individual. The study delegation log must reflect this (Appendix 1 SOP S-1006 Informed consent for research sponsored by UHL).

The definitions below should be used:

- **Not related** There is no evidence of causal relationship to the Investigational Device.
- **Related** There is evidence of causal relationship to the Investigational Device.
6. Safety Reporting Process

6.1 Safety reporting process for CE marked products used for their intended purpose and in-house proof of concept studies (Studies not requiring MHRA approval)

Assessment of Adverse Event
All adverse events must be reviewed by the CI/PI and categorised (Appendix 1) to determine whether the event is a device related event and the seriousness of the event.

Adverse Events/Adverse Device Effects (AE/ADEs)
AE/ADEs defined as non-serious in nature must be recorded in the medical records and the Adverse Event/Device Effect record (Appendix 2) and retained with the Case Report Form (CRF), unless it forms part of the CRF and is agreed by the Sponsor. All AE and ADEs must be observed to ensure that they do not escalate to an SAE/SADE.

There are no requirements to report these events to the Sponsor or Regulatory Agencies unless the AE and/or laboratory abnormalities are identified as critical evaluations of the study.

Anticipated Serious Adverse Device Effect (ASADE)
If the event is classified as an anticipated effect, which by its nature, incidence severity or outcome has been previously identified in the risk analysis report and/or protocol. This event does not require reporting to the Sponsor or Regulatory Agencies but must be recorded in the medical records and the adverse event record (Appendix 2). This document must be retained with the case report form unless it forms part of the case report form and is agreed by the Sponsor.

Serious Adverse Events/Serious Adverse Device Effects (SAE/SADEs)
All SAEs/SADEs in studies sponsored by UHL must be reported to the Sponsor immediately and within 24 hours of the research team becoming aware of the event unless they are listed in the protocol/clinical investigation plan as expected events. UHL Serious Adverse Event/Device Effect Report Form C for medical device studies (Appendix 3) must be used. This form and associated completion guidance document are both available on the R&I Website. This form and any documents provided to the Sponsor in support of the SAE/SADE MUST NOT contain any patient identifiable data.

Unanticipated Serious Device Effect (USADE)
Where an event could be related to the medical device and is unanticipated in relation to the IB/Risk Analysis Report, the Investigator must report this event immediately or within 24hrs to the Sponsor/Manufacturer and to the Regulatory Agencies within the required timelines (see below). Where applicable in blinded studies, unblinding must occur to assess treatment assignment.
MHRA reporting requirements of a USADE
Device related events involving a CE marked device/proof of concept studies in a post market surveillance study are reportable to the MHRA Adverse Incident Centre [https://aic.mhra.gov.uk/](https://aic.mhra.gov.uk/).

REC reporting requirements of a USADE

Reports should be submitted to the REC immediately or within 15 days of the Chief Investigator becoming aware of the event using the Non CTIMP Safety report form published on the HRA website [http://www.hra.nhs.uk/](http://www.hra.nhs.uk/)

The Chief Investigator is required to include a report of the safety of participants in the annual progress report to the REC.

Individual reports will be reviewed by the REC at a subcommittee or committee meeting. Any requests for further information should be provided as applicable and a copy forwarded to the Sponsor.

Where applicable SAEs, SADE or USADEs which occur within UHL must be reported on the trusts electronic incident reporting system (Datix). Reporting of incidents must be carried out in accordance with the Trusts Incident and Accident reporting policy

Multi-Centre studies
SAEs and SADEs from all sites must be sent to the Sponsor utilising the multicentre serious adverse events/ serious adverse device effect line listing table (Appendix 4). Where sites are managed through a third party contractor e.g. a Clinical Trials Unit (CTU), it may be appropriate to make alternative arrangements for reporting. These arrangements will be specifically detailed in the third party agreement. All SAE/SADE reports will be reviewed by the Director of R&I at the monthly R&I Management Meeting.

Follow up reporting
Sign Off and Review for UHL Sponsored Studies
For UHL Sponsored studies, the Chief Investigator (CI) or Principal Investigator (PI) is responsible for the review and sign off of all serious adverse event/effects. In the event that the CI/PI is unable to sign the report immediately, the research team/site should not delay sending the report, however a CI/PI signed copy must be forwarded to R&I as soon as possible. The research team/site must provide any additional information actively following up the subject until either:

- The SAE/USADE resolves, or
- Until 30 days after the discontinuation of use of the medical device

After discussion with, and in agreement by the Sponsor, it may be possible for additional medically qualified individuals to be delegated the responsibility for reviewing and signing off the SAE form.
6.2 Safety reporting process for Non-CE marked devices or CE marked devices used outside their intended use(s) (Studies requiring MHRA Approval)

Assessment of Adverse Events
All adverse events must be reviewed by the CI/PI and categorised (Appendix 1) to determine whether the event is a device related event and the seriousness of the event.

Each AE must be assessed for seriousness, causality, severity and expectedness. Where there are two assessments of causality, for example, the CI/PI assessment do not concur, the causality made by the Investigator cannot be downgraded.

Adverse events (AE) or Adverse Device Effect (ADE)
AE/ADEs defined as non-serious in nature must be recorded in the medical records and the Adverse Event/Device Effect record (Appendix 2) and retained with the case report form (CRF), unless it forms part of the CRF and is agreed by the Sponsor. All AE and ADEs must be observed to ensure that they do not escalate to an SAE/SADE.

There are no requirements to report these events to the Sponsor or Regulatory Agencies unless the AE and/or laboratory abnormalities are identified as critical evaluations of the study.

Serious Adverse Event / Serious Adverse Device Effects (SAE/SADEs)
All SAEs/SADEs in studies sponsored by UHL must be reported to the Sponsor immediately and within 24 hours of the research team becoming aware of the event unless they are listed in the protocol клинического исследования плана как ожидаемые события. UHL Serious Adverse Event/Device Effect Report Form C for medical device studies (Appendix 3) must be used. This form and associated completion guidance document are both available on the R&I Website. This form and any documents provided to the Sponsor in support of the SAE/SADE MUST NOT contain any patient identifiable data

Anticipated Serious Adverse Device Effect (ASADE)
If the event is classified as an anticipated effect, which by its nature, incidence severity or outcome has been previously identified in the risk analysis report and/or Protocol. This event does not require reporting to the Sponsor or Regulatory Agencies but must be recorded in the medical records and the adverse event record (Appendix 2). This document must be retained with the case report form unless it forms part of the case report form and is agreed by the Sponsor.

Unanticipated Serious Adverse Device Effect (USADE)
Where an event could be related to the medical device and is unanticipated in relation to the IB/Risk Analysis Report, the Investigator must report this event immediately or within 24hrs to the sponsor/manufacturer and to the regulatory agencies within the required timelines (see below). Where applicable in blinded studies, unblinding must occur to assess treatment assignment.
The USADE must be reported to the regulatory authorities without unjustified delay, not exceeding the timelines as indicated in the MHRA reporting Timeline Table (Appendix 5).

MHRA reporting requirements

Any adverse incident involving a medical device undergoing clinical investigation should be reported to the manufacturer, or directly to the Medicines & Healthcare Products Regulatory Agency via the online system: https://yellowcard.mhra.gov.uk/

The device must not be returned to the manufacturer until the MHRA has been given the opportunity to carry out/complete an investigation, the device should not be:

- discarded
- repaired
- returned to the manufacturer

All material evidence i.e. devices/parts removed, replaced or withdrawn from use following an incident, instructions for use, records of use, repair and maintenance records, packaging materials, or other means of batch identification must be:

- clearly identified and labelled
- stored securely

Evidence should not be interfered with in any way except for safety reasons or to prevent its loss. Where appropriate, a record should be made of all readings, settings and positions of switches, valves, dials, gauges and indicators, together with photographic evidence and eyewitness reports.

N.B: Consideration should be given to the practicality and implications of quarantining the device; for example if the device is an implantable device all further supplies of the device should be quarantined as a precaution until further advice is sought.

The Investigator and the Sponsor will undertake any requirements outlined in the MHRA investigation and follow up as instructed.

REC reporting requirements

Reports should be submitted immediately or within 15 days of the Chief Investigator becoming aware of the event using the Non CTIMP Safety report form to the REC published on the HRA website http://www.hra.nhs.uk/

The Chief Investigator is required to include a report of the safety of participants in the annual progress report to the REC.

Individual reports will be reviewed by the REC at a subcommittee or committee meeting. Any requests for further information should be provided as applicable and a copy forwarded to the Sponsor.

Where applicable SAEs, SADE or USADEs which occur within UHL must be reported on the trusts electronic incident reporting system (Datix). Reporting of incidents must be carried out in accordance with the Trusts Incident and Accident reporting policy.
Follow up reporting

Sign Off and Review for UHL Sponsored Studies
For UHL Sponsored studies, the Chief Investigator (CI) or Principal Investigator (PI) is responsible for the review and sign off of all serious adverse event/effects. In the event that the CI/PI is unable to sign the report immediately, the research team/site should not delay sending the report, however a CI/PI signed copy must be forwarded to R&I as soon as possible. The research team/site must provide any additional information actively following up the subject until either:

- The SAE/USADE resolves, or
- Until 30 days after the discontinuation of use of the medical device.

After discussion with, and in agreement by the Sponsor, it may be possible for additional medically qualified individuals to be delegated the responsibility for reviewing and signing off the SAE form.

Multi-Centre studies
All SAEs and SADeS from all sites must be sent to the Sponsor unless alternative arrangements have been agreed with the Sponsor. Where sites are managed through a third party contractor e.g. a Clinical Trials Unit it may be appropriate to make alternative arrangements for reporting. These arrangements will be specifically detailed in the third party agreement. All SAE/SADE will be reviewed by the Director of R&I at the monthly R&I Management Meeting. Should a USADE be reported at any site the Sponsor will delegate the responsibility of informing all principal Investigators involved in the study. Where required all medical devices at all sites will be quarantined until the MHRA investigation has been completed.

7. Documentation

The following documentation must be available in the Trial Master File (TMF)/Investigator Site File (ISF):

- SAE, SADE, USADE reports and follow-up information
- Adverse event/device effect document (Appendix 2)
- Evidence of submission and receipt of SAE/SADEs to the Sponsor and regulatory agencies within the required timeframe
- Evidence of timely USADE submission to the MHRA and main REC

The investigator must ensure that all SAE/SADE/USADE information is recorded accurately in the medical notes and the study CRF.

8. SAE/SADE/USADE Review Process

Acknowledgement will be issued to the Investigator from the Sponsor via email within 7 days of receipt of a fully completed form, and this must be filed in the TMF / ISF.
Each SAE/SADE/USADE will be registered on the recognised Sponsor database and reviewed by the Sponsor or their delegate, as per Appendix 6 (Medical device SAE/SADE review process flowchart). This review may lead to queries being issued by the Sponsor/delegate to request signed documentation, clarify information or complete outcome event. All queries will be sent via email and must be responded to within the stated timeframe as per the SAE/SADE Template Email (Appendix 7).

All SAE/SADE/USADE reported to the Sponsor will be reviewed at the R&I Management Meeting by the Director of R&I.

9. Non-Compliance

Where evidence of non-compliance is identified the Non-Compliance SOP S-1016 UHL will be followed. Corrective actions will be expected in accordance with MAJOR findings.

10. Responsibilities

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<tr>
<th>Responsibility</th>
<th>Undertaken by</th>
<th>Activity</th>
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</thead>
<tbody>
<tr>
<td>1 CI/PI/Delegated individual</td>
<td>CI/PI/Delegated individual</td>
<td>Report all serious adverse events/device effects to the Sponsor (except those identified as exempt)</td>
</tr>
<tr>
<td>2 CI/PI/Delegated Individual</td>
<td>CI/PI/Delegated individual</td>
<td>Follow up the initial report with a detailed written follow up/final report if not all information is available at the time of initial reporting.</td>
</tr>
<tr>
<td>3 CI/Delegated Individual</td>
<td>CI/Delegated Individual</td>
<td>Completion of adverse event/adverse device effect record/and or line listing and review and sign off by Chief Investigator.</td>
</tr>
<tr>
<td>4 CI/PI/Delegated individual</td>
<td>CI/PI/Delegated individual</td>
<td>Supply the Sponsor, MHRA and the main REC with any additional information requested.</td>
</tr>
<tr>
<td>5 Sponsor</td>
<td>Sponsor</td>
<td>Ensures that all USADEs are reported to the MHRA and REC within mandatory timelines.</td>
</tr>
<tr>
<td>6 Sponsor</td>
<td>Sponsor</td>
<td>Monitor all SAE/SADE line listings reported on a monthly basis to identify and if necessary act upon any emerging safety issues.</td>
</tr>
<tr>
<td>7 Sponsor</td>
<td>Monitor</td>
<td>The Monitor will review SAE/SADE submissions and request further clarification/information as required to ensure SAE/SADE report completion. The CI/PI will be provided with Sponsor acknowledgement of receipt of the completed SAE/SADE.</td>
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This table is used to track the development and approval of the document and any changes made on revised / reviewed versions.

### DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT

<table>
<thead>
<tr>
<th>Author / Lead Officer:</th>
<th>Julie James</th>
<th>Job Title: Clinical Trial Monitor and Trainer</th>
</tr>
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<tr>
<td>Reviewed by:</td>
<td>UHL Research Management Meeting</td>
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<tr>
<td>Approved by:</td>
<td>Professor Nigel Brunskill</td>
<td>Date Approved:</td>
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### REVIEW RECORD

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<tr>
<td>October 2017</td>
<td>1</td>
<td>Carolyn Maloney</td>
<td>New Standard Operating Procedure</td>
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### DISTRIBUTION RECORD:

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Version 1 October 2017

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