Standard Operating Procedure R&D/SOP011

Safety Reporting for Medical Device Trials

1. Scope

This SOP applies to staff involved with Cambridge Sponsored Clinical Investigations of Medical Devices (CIMDs).

2. Purpose

To describe the process for identifying, recording and reporting Adverse Device Effects (ADEs) and Serious Adverse Device Effects (SADEs) and other safety events according to the requirements of Good Clinical Practice (GCP) and the Medical Device Regulations 2002/618 and subsequent amendments.

To clarify the roles and responsibilities in this process

3. Definitions and Abbreviations

The headings below contain the definitions of terms and meaning of abbreviations used within the document.

3.1. Definitions

Term	Definition
Cambridge Sponsored	Sponsored by Cambridge University Hospitals NHS Foundation Trust (CUH); or the University of Cambridge (UoC); or jointly by CUH and UoC OR Sponsored by: Cambridge University Hospitals NHS Foundation Trust (CUH) or CUH jointly with the University of Cambridge or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Investigational Medical Device	Medical device being assessed for safety or performance in a clinical investigation. This includes devices already on the market being evaluated for a new intended use, new populations, new materials or design changes.
Adverse Device Effect	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, deployment, implantation, installation, operation, or any malfunction, a use error or intentional misuse
Serious Adverse Device Effect	SADE: (For the purposes of this SOP) these are ADEs that has resulted in any of the characteristics of an SAE, restricted to events related to the investigational medical device that: -led to a serious deterioration in health -resulted in a life threatening illness or injury, (Life-threatening refers to an event where 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 -resulted in a permanent impairment of a body structure or a body function, -required in-patient hospitalisation or prolongation of existing hospitalisation,(Any hospitalisation that was planned prior to randomisation will not meet SADE criteria. Any hospitalisation that is planned post randomisation, will meet the SADE criteria) -resulted in medical or surgical intervention to prevent life threatening illness or injury or resulted in persistent or significant disability or incapacity -led to foetal distress, foetal death or a congenital abnormality or birth defect. This includes device deficiencies that might have led to a serious adverse event if: -suitable action had not been taken -intervention had not been made -circumstances had been less fortunate A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.
Unanticipated Serious Adverse Device Effect	USADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment or protocol
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling

3.2. Abbreviations

Abbreviation	Meaning
SAE	Serious Adverse Event
ADE	Adverse Device Effect
CIMDs	Clinical Investigations of Medical Devices
MHRA	Medicines and Healthcare Products Regulatory Agency
SADE	Serious Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

4. Undertaken by

- The Investigator or delegated member of investigation team is responsible for identifying and reporting ADEs and other safety events as detailed in this procedure
- The Sponsor (CUH R&D office) is responsible for medical device vigilance reporting to the Regulatory Authority
- Responsibility of certain aspects of device vigilance may be delegated by the Sponsor to the Investigator by mutual agreement before the start of the investigation

- Reporting to the Research Ethics Committee is the responsibility of the Chief Investigator in conjunction with the Sponsor
- In the event that CUH and UoC agrees to co-sponsor a CIMD with another organisation, the responsibility for medical device vigilance must be agreed between the organisations before the trial commences and should be clearly documented in a clinical trial agreement or equivalent

5. Items Required

- R&D/FRM004 Medical Device Reporting form
- R&D/FRM003 Medical Device Trial Safety Reporting Form
- CCTU/SOP002 Pharmacovigilance Process for Investigator Teams
- CCTU/SOP029 Data Transfer

6. Summary of Significant Changes

Removal of link to Trust Risk Assessment Tool

Removal of links to websites that no longer work

7. Method

The following sections provide a description of the processes to be followed when implementing this document's procedures.

7.1. Identifying ADEs

- The CUH Risk Assessment tool will be used by the sponsor to determine the level of risk for the proposed investigation
- Based on the result of the risk assessment the design of the protocol agreed with the Sponsor should define clearly:
    - Which ADEs are recorded, and which are notified and reported
    - How ADEs are identified
    - The procedure for notifying the Investigator of such adverse events
    - Information on other adverse events not related to the device such as:
- SAEs
- Investigational Medical device deficiency that might have led to a SAE if:
    - Suitable action had not been taken
    - Intervention had not been made
    - Circumstances had been less fortunate
    - New findings /updates in relation to already reported events
- The member of the research team with delegated responsibility for identifying ADEs must be recorded on the delegation log
- ADEs should be recorded from the time the participant signs the consent form to take part in the clinical investigation
- ADEs may also be identified by support departments.

7.2. Recording ADEs, SADEs and Device Deficiencies

- The protocol should define exactly which adverse effect data points to record
- The ADE and SADE pages of the Case Report Forms (CRFs) or equivalent must be designed accordingly
- ADE and SADE data will be recorded in the CRF by a member of the research team with delegated responsibility to do so
- ADEs and SADEs are followed up according to the protocol or until resolution or death of the research participant
- The R&D Safety Reporting Form R&D/FRM 003 should be used

7.3. Assessment of Adverse Events

- For randomised double blind studies, any AE will be assessed as though the research participant was subjected to the device
- Each AE must be assessed for causality, seriousness, severity and expectedness by the Principle Investigator or delegate
- The assessment will be made as to whether the AE is likely to be related to the device according to the following definitions:

Unrelated:

- where an event is not considered to be related to the device –> For Non CTIMPs follow point 7.10 for CTIMPs follow CCTU/SOP002 Pharmacovigilance Process for Investigator Teams

Possibly Related:

- The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the ADE has a causal relationship to the device -> if this is the case follow point 7.4 onwards.

7.4. Assessment of Seriousness

Adverse events related to the investigational medical device (ADEs) are a Serious Adverse Device Effect (SADE) if it:

- Led to a death,
- Led to a serious deterioration in health
- Resulted in a life threatening illness or injury, (Life-threatening refers to an event where 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)
- Resulted in a permanent impairment of a body structure or function
- Required an in-patient hospitalisation or prolongation of existing hospitalisation, (any hospitalisation that was planned prior to randomisation or study treatment will not meet SADE criteria and will be defined in the protocol. Any hospitalisation that is planned post randomisation or study treatment, will meet the SADE criteria)
- Resulted in medical or surgical intervention to prevent life threatening illness or injury or resulted in persistent or significant disability or incapacity
- Led to foetal distress, foetal death, congenital abnormality or birth defect.

- This includes device deficiencies that might have led to a serious adverse event if:
    - suitable action had not been taken
    - intervention had not been made
    - circumstances had been less fortunate
- A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event

7.5. Severity

- If required by the protocol the Investigator will make an assessment of severity for each ADE
- Note: The term 'severe' used to describe the intensity of an event should not be confused with the term 'serious' which is a regulatory definition based on trial participant/event outcome action criteria.
- The assessment of severity is recorded on the CRF according to the following categories:

Mild:

- an event that is easily tolerated by the research participant, causing minimal discomfort and not interfering with every day activities

Moderate:

- an event that is sufficiently discomforting to interfere with normal activities

Severe:

- an event that prevents normal everyday activities

7.6. Assessment of Expectedness

- The Investigator must make an assessment of expectedness of the ADE based on knowledge of the effect and any relevant product information
- The event will be classed as either:

Expected:

- the reaction is consistent with the effects of the device

Unexpected:

- the reaction is not consistent with the effect of the device

7.7. Reporting SADEs/USADEs and device deficiencies to the Sponsor

- Any SADE which is unexpected (USADE) must be reported
- SADEs, USADEs and device deficiencies are subject to expedited reporting requirements
- The protocol may define certain SADEs which are not subject to expedited reporting to the Sponsor
- SADEs, USADEs and device deficiency reports must be:
    - Reported to Sponsor or delegate within 24 hours of the investigator becoming aware of the event/effect (telephone, email)
    - Followed up as soon as possible with a signed report from the Investigator

  - Provide an assessment of causality at the time of initial reporting
  - Maintain the blind unless it is considered necessary to break the blind in the interest of research participant safety
  - Contain no patient identifiable information. If reports are received with identifiable data, the data will immediately be scored through with a black marker. Refer to CCTU/SOP029 Data Transfer
- The Sponsor or delegate will confirm receipt of the SADE, USADE or device deficiency report

7.7.1. Sponsors Responsibility

- On receipt of the SADE, USADE or device deficiency report, the Sponsor or delegate, will assess the report for completeness and to ensure the correct assessment has been made
- When the information supplied is incomplete the Sponsor or delegate will contact the Investigator and request the missing information
- It should be indicated on follow-up reports that this is follow-up information in respect of a previously reported event
- If it is not possible to supply any further detail this will be recorded on the Sponsor SADE database
- In the case of the event meeting SADE or USADE criteria, the Sponsor or delegate will ensure that all the correct reporting procedures are followed
- Records for SADE, USADE and device deficiency reports and any follow up information are kept in the Investigator Site File (ISF), the TMF and by the Sponsor) for oversight purposes
- Post-study USADEs that occur after the research participant has completed a clinical investigation are also notified by the investigator to the sponsor
- SADEs and USADEs will be documented on the R&D/FRM003 Medical Device Safety Reporting Form

7.8. Expedited Reporting of SADEs, USADEs and device deficiencies to the Research Ethics Committee and the Regulatory Authority

- The Sponsor representative is responsible for reporting all received SADEs and USADEs reports to the MHRA
- The Chief Investigator in conjunction with the Sponsor is responsible for reporting to the Research Ethics Committee (REC) when required
- Any SADEs/USADEs - which indicate an imminent risk which require prompt remedial action will be reported within 2 calendar days of awareness by the Sponsor
- Any other SADEs/USADEs will be reported within 7 calendar days of the Sponsor becoming aware.
- Report using the reporting form FRM004
- In the event of a blinded study, the blind will be broken before USADEs are reported to the REC and Licensing Authority
- The Sponsor, or designee will be responsible for breaking the blind to ensure that the blind design of the trial and trial team is maintained
- After discussion with the Sponsor, if the event fits the criteria of a SAE, the Guidance for reporting to the REC for non-CTIMP trials will be followed:

http://www.hra.nhs.uk/research-community/during-your-research-project/safety-reporting/

7.9. Safety Reporting (Research other than CTIMPs)

- In research other than CTIMPs, a serious adverse event (SAE) is defined as an untoward occurrence that:
- (a) Results in death
- (b) Is life-threatening
- (c) Requires hospitalisation or prolongation of existing hospitalisation
- (d) Results in persistent or significant disability or incapacity
- (e) Consists of a congenital anomaly or birth defect
- (f) Considered medically significant by the investigator

An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:

Related – resulted from administration of any of the research procedures, and

Unexpected – the type of event not listed in the protocol as an expected

The Chief Investigator should include a report on the safety of participants in the annual progress report

Type	Who	When	How	To Whom
SAE	Chief Investigator or sponsor	Within 15 days of the CI becoming aware of the event.	SAE report form FRM004	Main REC for the study
Urgent safety Measures	Chief Investigator or sponsor. Or exceptionally by local Principal Investigator	(i) Immediately. (ii) Within 3 days.	By telephone (ii) Notice in writing setting out the reasons for the urgent safety measures and the plan for further action	Main REC for the study REC Co-ordinator will acknowledge within 30 days If notified by PI, relevant local REC should also be informed

7.10. Other Reporting Requirements

- In multi-centre studies the Sponsor/delegate is responsible for informing Investigators at participating sites of any reported USADEs and other safety information
- This can be delegated to a coordinating unit/group/individual
- USADEs sent directly to the Investigator from other studies of the same device must be reviewed by the Investigator and acted upon if appropriate
- Copies of USADE reports must be kept in the ISF, TMF and by the Sponsor
- For multi-centre studies in other member states, the Sponsor may authorise the local research team in that member state to submit the notification to
- the National Competent Authority and this will be outlined prior to the commencement of the study at that site

7.11. External Contracting of SADE and USADE Reporting

- Expedited reporting may be contracted to an external facility for individual studies. They will perform these tasks without contradiction to this SOP
- The facility will report all SADE and USADEs received from Investigators to the Sponsor as soon as the facility is first aware of the event
- All relevant follow-up information should be submitted to the Sponsor

8. Monitoring Compliance with and the Effectiveness of this Document

a. Process for Monitoring Compliance and Effectiveness

As part of routine monitoring visits, audit and inspection

b. Standards/Key Performance Indicators

This process forms part of a quality management system and is reviewed according to CCTU procedures. Standard Operating Procedures are reviewed every two years.

9. References

The Institute of Clinical Research, Abbreviations used in Clinical Trials.

Guidelines on medical Devices- Clinical Investigations: SAE reporting under Directives 90/385EEC and 93/42/eec (MEDDEV 2.7/3/DEC 2010)

Clinical investigations of medical devices – guidance for manufacturers; NOV2013; MHRA Guidance on legislation

Clinical investigations of medical devices – guidance for investigators; NOV2013; MHRA guidance on legislation

10. Associated Documents

NA

11. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

12. Disclaimer

It is the user's responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

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