STANDARD OPERATING PROCEDURE FOR IDENTIFYING, RECORDING AND REPORTING ADVERSE EVENTS FOR CLINICAL INVESTIGATIONS OF MEDICAL DEVICES

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1. PURPOSE

This document describes the procedure used for identifying, recording and reporting Adverse Events (AEs) occurring in Clinical Investigations of Medical Devices (CIMDs) and complies with the requirements of the Medical Device Regulations 2002/618 and Good Clinical Practice (GCP).

It is the responsibility of all researchers using this SOP to ensure they are using the latest version of it. The latest version is available via the R&D pages on the NHS Fife Intranet (www.nhsfife.org/research). For guidance, contact the R&D Department via fife-uhb.randd@nhs.net.

2. APPLICABILITY

This SOP applies to all staff involved in the conduct of a CIMD hosted by NHS Fife.

3. POLICY

3.1 It is essential that all adverse events which occur during the course of a participant's involvement in a research project are appropriately recorded and reported in order to ensure their continuing safety.

3.2 The specific reporting requirements for each CIMD will differ, depending on the nature of the CIMD and the patient population. The decision on what Adverse Event data to record must be made by the trial Sponsor. NHS Fife staff working on externally sponsored CIMDs must follow the SOPs of the Sponsor organisation (where provided) and/or the procedures outlined in the trial protocol or other trial specific document relating to the identification, reporting and recording of Adverse Events.

3.3 The Principal Investigator (PI) has responsibility for the trial within NHS Fife and for informing the Chief Investigator (CI) of all AEs that occur and for maintaining records of AEs, as specified in the trial protocol.

3.4 Adverse Events (AEs) must be recorded from the time a participant signs the consent form to take part in the trial, unless otherwise defined in the protocol.

3.5 As well as trial related Adverse Events, Adverse Incidents may occur on CIMDs. It is important that research related Adverse Incidents are reported in the same way as non-research related Adverse Incidents (see Section 5.7).

4. DEFINITIONS

4.1 Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in a subject enrolled into a trial, whether or not related to the Investigational Medical Device. This includes events related to the Investigational Device or the comparator and events related to the procedures.

4.2 Adverse Device Effect (ADE)

An ADE is an AE 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 a 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.

4.3 Serious Adverse Event (SAE).

An SAE is defined as serious if it:

- results in death
- is a life threatening* illness or injury
- requires inpatient hospitalisation^ or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- requires medical or surgical intervention to prevent any of the above
- leads to foetal distress, foetal death or consists of a congenital anomaly or birth defect
- Any other significant medical occurrence considered serious by the Principal Investigator (PI) or delegate.

A planned hospitalisation for a pre-existing condition, or a procedure required by the Clinical Investigation Plan (CIP), without a serious deterioration in health, is not considered to be a serious adverse event.

***** *Life-threatening in the definition of an SAE 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.*

^ *Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation, will meet the SADE criteria.*

4.4 Serious Adverse Device Effect (SADE)

A SADE is an AE that has resulted in any of the consequences characteristic of an SAE (see Section 4.3). This includes device deficiencies that might have led to a SAE if:

- Suitable action had not been taken
- Intervention had not been made
- If circumstances had been less fortunate

4.5 Anticipated Serious Adverse Device Effect (ASADE)

An ASADE is a Serious Adverse Device Effect which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report or Clinical Investigation Plan.

4.6 Unanticipated Serious Adverse Device Effect (USADE)

A USADE is 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 Clinical Investigational Plan.

4.7 Device Deficiency

A Device Deficiency is an 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.

5. PROCEDURE

5.1 Identifying Adverse Events

5.1.1 All members of the study team must be fully trained on the study specific Adverse Event reporting requirements.

5.1.2 Unless otherwise stated in the protocol, the PI (or delegated member of the research team) should ask the study participants at each study visit about hospitalisations, consultations with other medical practitioners, disability or incapacity or whether any other AEs have occurred since their previous visit.

5.1.3 AEs may also be identified by Support Departments, for example, clinical biochemistry, haematology, and radiology.

5.1.4 AEs may be identified through the R&D Trial Patient Alert Procedure which notifies the R&D Department about hospital admissions and/or the death of patients flagged as taking part in a clinical research study (see WI09(Fife) - R&D Trial Patient Alert Procedure).

5.2 Recording Adverse Events and Device Deficiencies

5.2.1 All Adverse Events must be recorded and reported in accordance with the requirements of the trial Sponsor.

5.2.2 In the event of an adverse event, the PI (or delegated member of research team) must review all documentation (e.g., hospital notes, laboratory and diagnostic reports) relevant to the event. The PI (or delegated Physician) will make an assessment of intensity, causality, expectedness and seriousness. Detailed guidance on making this assessment is given in section 5.3.

5.2.3 Except where the protocol states otherwise, all adverse events/reactions should be recorded in detail to allow analysis at a later stage. In addition to completion of any study specific documentation, details of the AE must also be recorded in accordance with safety reporting guidance in the Protocol.

5.2.4 The investigator should keep an ongoing log of Adverse Events in the Investigator Site File (ISF) that must be made available to the Sponsor on request (See Doc Ref 19-01).

5.2.5 All AEs must be followed up until resolved, resolved with sequelae* or death of the trial participant.

** The signs/symptoms of the reported AE have not completely resolved and a new baseline for the subject/ patient is established since full recovery is not expected.*

5.3 Assessment of AEs

Each AE must be assessed for seriousness, causality and expectedness by the Principal Investigator (or delegated physician).

5.3.1 Seriousness

The PI (or delegated physician) must make an assessment of seriousness (as defined in Section 4.3).

5.3.2 Causality

The PI (or delegated physician) must use clinical judgement to determine the relationship between the use of the device and the occurrence of each adverse event. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors etc. must be considered.

5.3.3 Expectedness

If the AE is judged to be related to the device, the PI (or delegate) must make an assessment of expectedness based on knowledge of the reaction and any relevant product information as documented the risk analysis report. The event will be classed as either;

- Expected: the reaction is consistent with the effects of the device listed in the risk analysis report.
- Unexpected: the reaction is not consistent with the effects listed in the risk analysis report.

5.4 Reporting SAEs/SADEs/USADEs and Device Deficiencies to the Sponsor

5.4.1 The PI (or delegate) is responsible for the prompt reporting of SAEs, SADEs, USADEs and Device Deficiencies to the Sponsor in writing, within 24 hours of becoming aware of the event.

5.4.2 SAEs, SADEs, USADEs and Device Deficiencies must be reported using the study specific reporting forms provided by the Sponsor.

5.4.3 Reporting forms must be as complete as possible, must provide an assessment of causality and expectedness and must be signed and dated by the PI (or delegate). An initial report should be submitted as soon as is possible. It is not reasonable to delay reporting until all the required information is available. If pertinent information is not available at the time of reporting, the PI (or delegate) must ensure that any missing information is provided in a follow-up report as soon as this becomes available.

5.4.4 SAE/SADE/USADE reporting to the Sponsor should maintain the study blinding unless it is considered necessary to unblind in the interest of participant safety.

5.4.5 Participant identifiable information other than that determined as acceptable by the Sponsor must not be included on the SAE reporting form.

5.4.6 Copies of all SAE/SADE/USADE Reporting Forms sent to the Sponsor must be retained in the Investigator Site File (ISF).

5.5 Urgent Safety Measures

5.5.1 The Sponsor and PI may take appropriate urgent safety measures in order to protect the participants of a CIMD against any immediate hazard to their health or safety.

5.5.2 Urgent safety measures can be implemented immediately after becoming aware of the hazard.

5.5.3 The PI must phone the Sponsor and discuss the issue immediately after becoming aware of the hazard.

5.6 Reporting USADEs to NHS Fife R&D

5.6.1 The PI(or delegate) must also notify the NHS Fife R&D Department of any USADEs immediately by email to: fife-uhb.randd@nhs.net. On receipt of such a notification, the R&D Department will liaise closely with the PI to ensure that the necessary action is taken.

5.7 Reporting Adverse Incidents

5.7.1 In the same way that adverse incidents, including clinical, non-clinical and near misses can involve patients, staff and visitors during routine care, adverse incidents can also occur during research related activities. It is important that research related Adverse Incidents are treated in the same way as non research related Adverse Incidents.

5.7.2 Events that are both Adverse Incidents and Adverse Events MUST be reported independently following both the procedure for AE reporting and the procedure for AI reporting.

5.7.3 All Adverse Incidents that are reported as occurring on research trials taking place in NHS Fife must be reported via DATIX (see NHS Fife Policy GP/I9 - Adverse Events).

6. ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event .
CI	Chief Investigator
CIMD	Clinical Investigation of a Medical Device
CRF	Case Report Form
GCP	Good Clinical Practice
PI	Principal Investigator
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
USADE	Unexpected Serious Adverse Device Effect

7. ASSOCIATED DOCUMENTS

Doc Ref 32-01 – Adverse Event Log
WI09(Fife) - R&D Trial Patient Alert Procedure

8. REFERENCES

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.
(https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)

Medical Devices Regulations 2002 (SI 2002 No 618, as amended)
(http://www.legislation.gov.uk/uksi/2002/618/contents/made)
It is assumed that by referencing the principal regulations, all subsequent amendments made to the principal regulations are included in this citation.

9. DOCUMENT HISTORY

Version Number	Edited by (job title)	Effective Date	Details of Revisions Made
1	Julie Aitken R&D Trials Facilitator	02/02/2015	New - Adapted from ACCORD SOP CR012
2	Julie Aitken R&D Trials Facilitator	26/02/2019	Reformatted in line with current SOP template, revised to cover 'hosted' CIMDs only and to reflect current practice.

10. APPROVAL

APPROVED BY	Date
Professor Alex Baldacchino, Research & Development Director, NHS Fife Signature: 	26/02/2019