STANDARD OPERATING PROCEDURE FOR IDENTIFYING, RECORDING AND REPORTING ADVERSE EVENTS FOR CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS (CTIMPs)

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ISSUE DATE:	**26/02/2019**
EFFECTIVE DATE:	**26/02/2019**
REVIEW DATE:	**26/02/2021**

1. PURPOSE

This document describes the procedure for identifying, recording and reporting adverse events and reactions occurring in Clinical Trials of Investigational Medicinal Products (CTIMPs which are being hosted by NHS Fife. It complies with the principles of 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

Unless otherwise specified this document applies to all staff working on CTIMPs hosted by NHS Fife.

3. POLICY

3.1 It is essential that all Adverse Events (AEs) which occur during the course of a participant's involvement in a CTIMP are appropriately recorded and reported in order to ensure continuing safety.

3.2 The specific reporting requirements for each trial will differ, dependent on the nature of the trial 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 CTIMPs must follow the SOPs of the Sponsor organisation (where provided) and/or the procedures outlined in the study protocol or other study 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 study protocol.

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

3.5 As well as trial related Adverse Events, Adverse Incidents may occur on clinical trials. It is important that research related Adverse Incidents are

reported in the same way as non-research related Adverse Incidents (see Section 5.8).

4. DEFINITIONS

4.1 Adverse Event (AE)

Any untoward medical occurrence in a study participant (e.g. abnormal laboratory findings, unfavourable symptoms or diseases) which may or may not have a causal relationship with the study treatment or procedure.

4.2 Adverse Reaction (AR)

Any untoward and unintended response that has occurred due to a study treatment or procedure where there is evidence or argument to suggest a causal relationship.

4.3 Unexpected Adverse Reaction

An event where there is evidence to suggest a causal relationship and when the type of event is not listed in the study protocol as an expected event.

4.4 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any AE or AR which:

- results in death
- is life threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- Any other significant medical occurrence considered serious by the Principal Investigator (PI) or delegate.

4.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected unexpected serious adverse reaction i.e. a SAR which is also 'unexpected', in that the type of event is not listed in the study protocol as expected.

4.6 Adverse Incident (AI)

Any incident/accident, near miss or untoward event which had or may have had the potential to cause harm, dissatisfaction or injury to persons, loss or damage to property. This includes hazards, accident, ill health, dangerous occurrences and near misses.

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 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

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

5.3 Assessment of Adverse Events

5.3.1 Causality

The PI (or delegated physician) must use clinical judgement to determine the relationship between the intervention/procedure/product 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.

Causality must be categorised as follows:

- Not related: Temporal relationship of the onset of the event, relative to administration of the intervention/procedure/product, is not reasonable or another cause can by itself explain the occurrence of the event.

- Unlikely: Temporal relationship of the onset of the event, relative to administration of the intervention/procedure/product, is likely to have another cause which can by itself explain the occurrence of the event.
- Possibly* related: Temporal relationship of the onset of the event, relative to administration of the intervention/procedure/product, is reasonable but the event could have been due to another, equally likely cause.
- Probably related*: Temporal relationship of the onset of the event, relative to administration of the intervention/procedure/product, is reasonable and the event is more likely explained by the product than any other cause.
- Definitely related*: Temporal relationship of the onset of the event, relative to administration of the intervention/procedure/product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

**Where an event is assessed as possibly related, probably related, definitely related, the event is an adverse reaction (AR).*

5.3.2 Seriousness

An event is considered serious if it meets one or more of the following criteria:

- 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
- Any other significant medical occurrence e.g. significantly deranged blood results.

5.3.3 Expectedness

The PI (or delegate) must assess the expectedness of all Adverse Reactions (AR) based on the product information documented in the Reference Safety Information (RSI) specified by the Sponsor (see section 5.3.4).

Adverse Reactions may be classed as either:

- **Expected**: the AR is consistent with the information on the adverse effects of the study drug listed in the RSI. An expected AR must be an event previously observed and documented.
- **Unexpected**: the AR is not consistent with the information on the adverse effects of the study drug listed in the RSI.

An Adverse reaction may be described as 'unexpected' if it has occurred with greater frequency or severity that might otherwise have been expected.

5.3.4 Reference Safety Information (RSI)

5.3.4.1 The RSI includes a list of all observed related adverse reactions (serious and non-serious), including a description of the nature of events, severity or grade as well as their frequency.

5.3.4.2 The RSI can change during the course of the trial and the PI must use the RSI contained in the Summary of Product Characteristics (SmPC) or

Investigators Brochure (IB) version which has been approved at the time of the event.

5.4 Reporting SAEs, SARs and SUSARs to the Sponsor

5.4.1 The PI (or delegate) must report all events which meet the criteria of Serious to the Sponsor, by email, of, within 24 hours of becoming aware of the event.

5.4.2 Once it has been confirmed that the event requires formal reporting and follow-up, all SAEs, SARs and SUSARs must be reported using the study specific reporting forms provided by the Sponsor.

5.4.3 SAE 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/SAR reporting to the Sponsor should maintain the blind 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 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 CTIMP 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 Pregnancy Reporting

5.6.1 Pregnancy is not usually considered an AE or SAE, however an abnormal outcome would be. For some trials it is considered an SAE and needs to be reported as such. For this reason the PI must collect pregnancy information for female trial participants or female partners of male trial participants who become pregnant while participating in a study.

5.6.2 For female partners of male trial participants who become pregnant while participating in a study, consent should be obtained to follow up the pregnancy.

5.6.3 The PI must record the information on a study specific reporting form and send this to the Sponsor within the timelines specified by the Sponsor.

5.6.4 Any pregnancy that occurs in a trial participant or a trial participant's partner during a trial should be followed to outcome. In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post delivery. Follow-up information should be recorded on a study specific form as specified by the Sponsor.

5.7 Reporting SUSARs To NHS Fife R&D

5.7.1 Where an SAE is considered to be a SUSAR then the PI(or delegate) must also notify the NHS Fife R&D Department 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.

5.8 Reporting Adverse Incidents

5.8.1 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.

5.8.2 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.

5.8.3 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. ASSOCIATED DOCUMENTS

Doc Ref 19-01 – Adverse Event Log
WI09(Fife) - R&D Trial Patient Alert Procedure

7. ABBREVIATIONS

AE	Adverse Event.
AI	Adverse Incident
AR	Adverse Reaction
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
IB	Investigators Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	Non Investigational Medicinal Product
PI	Principal Investigator
R&D	Research & Development
REC	Research Ethics Committee

SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

8. REFERENCES

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. (http://www.wma.net/e/policy/b3.htm)

Medicines for Human Use (Clinical Trials) Regulations 2004.
(*http://www.opsi.gov.uk/si/si2004/20041031.htm*)
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 TASC SOP 1, version 7
2	Julie Aitken R&D Trials Facilitator	26/02/2019	Reformatted in line with current SOP template, revised to cover 'hosted' CTIMPs only and to reflect current practice.

10. APPROVAL

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