STANDARD OPERATING PROCEDURE FOR IDENTIFYING, RECORDING AND REPORTING ADVERSE EVENTS FOR STUDIES HOSTED BY NHS FIFE

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1. PURPOSE

This document describes the procedure for identifying, recording and reporting adverse events and reactions occurring in studies being hosted by NHS Fife.

It is the responsibility of all staff using this SOP to ensure they are using the latest version of it. The latest version is available via StaffLink, the R&D section of the NHS Fife website (www.nhsfife.org/research) and EDGE (https://www.edge.nhs.uk). For guidance, contact the R&D Department via fife.randd@nhs.scot

2. APPLICABILITY

This document applies to all staff working on studies 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 study 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 study and the patient population. The decision on what Adverse Event data to record must be made by the study Sponsor. NHS Fife staff working on externally sponsored studies 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 study within NHS Fife, which includes ensuring that all members of the study team are fully trained on the study specific adverse event reporting requirements, 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 study related Adverse Events, Adverse Incidents (AIs) may occur during the course of a study. 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.

4.7 Reference Safety Information (RSI) for CTIMPs

4.7.1 The Reference Safety Information (RSI) is a list of medical events that defines which Adverse Reactions are expected for the Investigational Medicinal Product (IMP) being administered to clinical trial patients, and which therefore do not require expedited reporting to the Competent Authority. It includes a description of the nature of events, severity or grade as well as their frequency.

4.7.2 The study Sponsor is required to clearly define where the RSI can be found for a trial, for example the Investigator Brochure (IB) or Summary of Product Characteristics (SmPC). The entire IB or SmPC is not the RSI, but a clearly defined section within these documents. Investigators must confirm with the study Sponsor if there is any uncertainty as to where to locate the RSI or what the current version of the RSI is.

4.7.3 The RSI can change during the course of the trial and these changes must be submitted by the Sponsor as a substantial amendment.

4.7.4 The PI (or delegate) must use the RSI which has been approved at the time of the event to assess the expectedness of all SARs (see 5.3.3).

5. PROCEDURE

5.1 Identifying Adverse Events

5.1.1 The PI (or delegated member of the research team) must 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.

5.1.2 AEs may also be identified by Support Departments, for example, Clinical Biochemistry, Haematology, and Radiology.

5.1.3 AEs may also 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 R&D WI09 - R&D Trial Patient Alert Procedure).

5.2 Recording Adverse Events

5.2.1 All Adverse Events must be recorded in accordance with the requirements of the study Sponsor, on the study specific forms or eCRF provided by the Sponsor.

5.2.2 In the event of an Adverse Event, the PI (or delegated physician) must review all documentation (e.g., patient's medical records, laboratory and diagnostic reports) relevant to the event. The PI (or delegated Physician) must make an assessment of causality, expectedness and seriousness and this assessment must be documented in accordance with the procedure specified by the study Sponsor. Detailed guidance on making this assessment is given in Section 5.3.

5.2.3 Patient identifiable information other than that determined as required by the Sponsor must not be included on the AE report.

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

5.2.5 In addition to any study specific documentation and AE Log, details of all AEs must be recorded in the patient's medical record via the clinical notes section on TrakCare.

5.2.6 Where EDGE is being used by the local Research Team to manage the study, details of all SAEs must also be recorded as an 'Event' in the patient's record in EDGE.

5.2.7 Copies of all SAE Reporting Forms, correspondence between members of the local research team and correspondence with the Sponsor relating to the SAE must be retained in the Investigator Site File (ISF).

5.2.8 Where EDGE is being used by the local Research Team, copies of correspondence and SAE reporting forms must be uploaded to the patient's record on EDGE. Where data is entered directly onto the eCRF and there are not any reporting forms or correspondence to be uploaded to EDGE, then a comment must be added the event in EDGE.

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 IMP or study intervention 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. *Where an event is assessed as possibly related, probably related, or 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 current RSI specified by the Sponsor. 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.

Expectedness can have a lot of different meanings in the medical world, but from a Clinical Trial perspective, in relation to safety reports and Suspected Unexpected Serious Adverse Reactions (SUSARs), it means whether or not the reaction is an expected side effect of the IMP, thus determining whether it does or does not need reporting in an expedited fashion.

To be categorised as expected, the reaction must be clearly listed in the RSI. It does not mean:

- a reaction that is common in the patient population.
- a reaction commonly seen as part of the disease under investigation.
- a common effect of pre-study surgery.
- a common effect of any Non-IMPs the patient is taking.
- a reaction the investigator has no concerns about based on their previous experience using the IMP and the patient population.
- reactions that a review of the literature has indicated are not concerning.

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

5.4 Reporting Adverse Events

5.4.1 Reporting and follow-up of all AEs must be done in accordance with the procedures required by the Sponsor and specified in the study protocol, using the study specific reporting forms provided by the Sponsor.

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

5.4.3 An initial SAE report must be completed with the information that is available and 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 AE reporting to the Sponsor must maintain the blind unless it is considered necessary to unblind in the interest of patient safety.

5.5 Urgent Safety Measures

5.5.1 The Sponsor and PI must take appropriate urgent safety measures in order to protect the participants of a study 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 occurring in a participant or partner of a participant in a study is not considered an AE or SAE, however an abnormal outcome would be and therefore any pregnancy must be monitored and followed-up in accordance with the study protocol. This includes participants in a CTIMP who become pregnant at any stage where the foetus could have been exposed to the investigational medicinal product (e.g., if the active substance or one of its metabolites have a long half-life). In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post delivery.

5.6.2 Where Pregnancy reporting is required by the study protocol, the PI or delegate must collect all pregnancy information to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of birth defects, congenital abnormalities, or maternal and/or newborn complications.

5.6.3 Details of the pregnancy must be reported by the PI or delegate to the Sponsor on the study specific forms provided and within the timeline specified by the Sponsor.

5.6.4 In addition to reporting to the Sponsor, details of the reported pregnancy must be added as an 'Event' to the participants record on EDGE, where EDGE is being used by the local Research Team. If EDGE is not being used then a copy of the study specific reporting forms must be emailed to the NHS Fife R&D department (fife.randdtrial@nhs.scot).

5.6.5 Any pregnancy that results in an SAE must also be reported to the Sponsor in accordance with the Sponsor's requirements for SAE reporting (see section 5.4).

5.6.6 Where a trial participant's partner becomes pregnant while their partner is participating in a study, consent must be obtained from the pregnant partner to follow up the pregnancy.

5.7 Reporting SUSARSs to NHS Fife R&D

5.7.1 Where EDGE is not being used by the local Research Team to capture details of all SAEs (see 5.2) then a copy of the study specific SUSAR reporting forms must be emailed to the NHS Fife R&D Department (fife.randdtrial@nhs.scot).

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 available via StaffLink).

6. ASSOCIATED DOCUMENTS

R&D WI09 - R&D Trial Patient Alert Procedure

7. REFERENCES

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.

8. ABBREVIATIONS

AE	Adverse Event
AI	Adverse Incident
AR	Adverse Reaction
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
IB	Investigator Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
PI	Principal Investigator
R&D	Research & Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

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.

3	Julie Aitken R&D Quality & Performance Lead	04 Jun 2021	Title and content updated to cover all hosted studies, both CTIMP and Non-CTIMP. Process for using EDGE to track SAEs and Pregnancies and report them to NHS Fife R&D added. Further clarification on the definition of a SUSAR added. Further information relating to the Reference Safety Information (RSI) added.

10. APPROVAL

APPROVED BY	Date
Professor Alex Baldacchino, Research & Development Director, NHS Fife Signature: 	07 May 2021