STANDARD OPERATING PROCEDURE FOR IDENTIFYING, RECORDING AND REPORTING ADVERSE EVENTS FOR RESEARCH (OTHER THAN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS OR REGULATED CLINICAL INVESTIGATIONS OF MEDICAL DEVICES)

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1. PURPOSE

This document describes the procedure used for identifying, recording and reporting adverse events occurring in research (other than Clinical Trials of Investigational Medicinal Products (CTIMPs)), undertaken in NHS Fife and 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 Research & Development (R&D) pages on the NHS Fife Intranet (www.nhsfife.org/research) or for guidance, contact the R&D Office (fife-uhb.randd@nhs.net).

2. APPLICABILITY

This SOP applies to all members of a research team involved in the conduct of non-CTIMP studies sponsored or co-sponsored by NHS Fife.

This SOP does not describe the requirements for externally sponsored non-CTIMP studies hosted by NHS Fife. For these studies the external Sponsor's reporting procedure should be followed although there is an additional requirement to notify the R&D Office in the event of an SAE that is both unexpected and thought to be related (see Section 5.9).

3. POLICY

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

3.2 The specific reporting requirements for each research project will differ, dependent on the nature of the study and the patient population. The decision on what Adverse Event data to record must be the result of an assessment of the risk associated with the study, conducted at the time of sponsorship review (see SOP06(Fife) - Sponsor Agreement for Research Projects Involving Humans, Their Tissue and/or Data). The requirement to report a Pregnancy in a participant during the course of the study must also be assessed at this stage.

3.3 There is no requirement for recording of AE data for non-interventional, non-invasive studies (i.e. questionnaire based studies).

3.4 In all cases, for non-CTIMPs the study protocol must have a distinct section which states clearly what events are expected to be reported and what exceptions there may be in safety reporting. This section must include:

- which adverse events are to be recorded and reported
- how adverse events will be identified (e.g. by enquiry at study visits, from lab and radiology reports, medical records)
- how adverse events are to be recorded, e.g. in the CRF and/or patient records
- any type of event which is an expected occurrence and excluded from the reporting requirements

3.5 Where reporting requirements exist the following will apply:

- The Chief Investigator (CI) on behalf of the Sponsor has overall responsibility for the conduct of the study. In a multi-site study, the CI has co-ordinating responsibility for reporting adverse events to the Sponsor and must also ensure that all investigators are aware of safety reporting procedures and timelines and provide training where deemed necessary. The CI also takes overall responsibility for the submission of Annual Safety Report forms to the Sponsor and REC.
- The Principal Investigator (PI) has responsibility for the research at a local site. There should be one PI for each research site. In the case of a single-site study, the CI and the PI will normally be the same person. The PI is responsible for informing the CI of all SAEs that occur at their site and for maintaining records of AEs, as specified in the study protocol.
- The Research and Development Office (R&D) acting on behalf of the Sponsor has the responsibility for reporting adverse events to the Research Ethics Committee (REC) which issued the approval for the study, for ensuring that all adverse event documentation and Annual Safety Reports are passed to the designated clinical reviewer (Medical Director), collecting review outcomes from the Research Governance Group meetings and for keeping detailed records of all Investigator-reported adverse events.

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

3.7 At the conclusion of the study all adverse event/reactions recorded during a study must be subject to statistical analysis and that analysis and any subsequent conclusions must be included in the final study report.

3.8 As well as research related Adverse Events, Adverse Incidents may occur on research studies. 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 Non-Investigational Medicinal Product (NIMP)

Products that are not the object of investigation (for example drugs used as part of standard care) may be supplied to participants in the study and used in accordance with the protocol. This might be, for example, medicinal products such as support/rescue medication for preventative, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the participant. These medicinal products do not fall within the definition of Investigational Medicinal Product (IMP) in Directive 2001/20/EC and are called Non-Investigational Medicinal Products (NIMPs).

4.2 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.

4.3 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.

4.4 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.

4.5 A 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
- or is otherwise considered serious by the Principal Investigator (PI) or delegate.

4.6 A 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.

4.7 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 and Recording 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 For the majority of studies, the Investigator (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. Where notification of such abnormal values or measurements would not occur as standard clinical practice, the procedure for notifying the investigator (or delegate) must be clearly documented prior to the start of the study.

5.1.4 In the event of an adverse event, the investigator (or delegated member of research team) must review all documentation (e.g., hospital notes, laboratory and diagnostic reports) relevant to the event. The investigator will make an assessment of intensity, causality, expectedness and seriousness. Detailed guidance on making this assessment is given in section 5.2.

5.1.5 Except where the protocol states otherwise, all adverse events/reactions should be recorded in detail to allow analysis at a later stage. A template for recording Adverse Events is provided (See Doc Ref 31-01) or alternatively AEs may be recorded in the Case Report Form. It is also advisable that adverse events are recorded in the patient's medical notes where possible and that this includes the assessment of causality, severity and seriousness.

5.1.6 The investigator should keep an ongoing log of adverse events in the ISF that must be made available to the Sponsor on request (See Doc Ref 31-02).

5.2 Assessment of Adverse Events

5.2.1 Assessment of an adverse event is a medical decision and as such **MUST** only be performed by a medically qualified team member. This may not be the PI if they are not medically qualified.

5.2.2 For randomised, double blind studies, AEs should be assessed as though the study participant was randomised to the study intervention.

5.2.3 Intensity

The assessment of intensity will be based on the investigator's clinical judgement using the following definitions:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities.

Note: The term severity is often used to describe the intensity of a specific event. This is not the same as 'seriousness', which is a regulatory definition based on study participant/event outcome action criteria. For example, a headache may be severe but not serious, while a minor stroke may be serious but is not severe.

5.2.4 Causality

The investigator will 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).*

The assessment of causality made by the PI (or delegate) cannot be downgraded by either the Sponsor or the Chief Investigator (CI). In the case of a difference of opinion both assessments must be recorded and the 'worst case' assessment used for reporting purposes.

5.2.5 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

5.2.6 Expectedness

Adverse reactions must be considered as unexpected if they add significant information on the specificity or severity of an expected adverse reaction. An Adverse reaction may be described as 'unexpected' if it has occurred with greater frequency or severity that might otherwise have been expected.

The expectedness of an adverse reaction shall be determined according to the protocol or other reference documentation.

- Expected: Reaction previously identified and described in protocol and/or reference documents
- Unexpected: Reaction not previously described in the protocol or reference documents.

NB The protocol must identify the reference documentation used.

5.3 Reporting Serious Adverse Events

5.3.1 Immediately after becoming aware of a Serious Adverse Event (and within 24 hours) a member of the research team must notify the NHS Fife R&D Department. Written reports should be made by completing a SAE/SUSAR Initial Report Form (Doc Ref 31-03) or study specific form if available. The only exception is where the protocol identifies the event as not requiring immediate reporting.

5.3.2 The initial report must include as much information as is available at the time and should be signed by a suitable qualified medical doctor, usually the PI or delegated investigator, to confirm their review and assessment of the SAE. This form must be emailed to the NHS Fife R&D Department to fife-uhb.randd@nhs.net.

Participant identifiable information other than date of birth, gender and study number should not be included on the SAE reporting form.

For the avoidance of doubt, the date that the initial notification is issued to the NHS Fife R&D Department is Day 0 of the reporting timescales.

5.3.3 The NHS Fife R&D Department will acknowledge receipt of the SAE notification by noon of the following working day. If acknowledgement of the

SAE is not received by the Investigator by this time then it is the responsibility of the Investigator to contact the NHS Fife R&D Department immediately.

5.3.4 The investigator (or delegated person) must provide any information missing from the initial report within five working days of the initial report to the R&D Department.

5.3.5 After the initial report, the investigator is required to actively follow-up the participant until either the SAE resolves, it is resolved with sequelae, the study participant dies or the Sponsor and CI/PI agree that no further follow-up is required. This decision must be documented in the SMF/ISF.

5.3.6 The Investigator (or delegated person) must provide follow-up information, each time new information is available, using an SAE/SUSAR Follow-up Report Form (Doc Ref 31-04) or study specific form where available.

5.3.7 Copies of all SAE reporting forms sent to the R&D Department must be retained in the Investigator Site File.

5.4 Expedited Reporting of SUSARs to the Research Ethics Committee (REC).

5.4.1 If a research participant experiences an SAE and the CI/PI determines the event to have been 'possibly, probably or definitely related' and 'unexpected', additional expedited onward reporting requirements exist and the R&D Office must (on behalf of the Sponsor) notify the REC which issued approval for the study within 15 days of becoming aware of it.

The R&D Office reserves the right to delegate this responsibility to the CI and this decision will be documented.

SUSARs must be reported to the REC which issued the approval for the study using the NRES SAE Reporting Form for non-CTIMPs from the NRES website - http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/.

Note: For non-CTIMP studies, although there is no requirement for onward expedited reporting for SAEs that are not deemed to be related to the intervention and unexpected, they must be documented in the Annual Progress Reports to the REC (see SOP08(Fife) - Preparing & Submitting Progress & Safety Reports).

5.5 Expedited reporting of other events

5.5.1 The following safety issues should also be reported by the CI/PI to the Sponsor in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of expected SAR, which is judged to be clinically important.
- Related and Unexpected SAEs that occur after the trial participant has completed a study and are notified to the CI/PI.

5.5.2 The Sponsor is responsible for informing the REC of all safety issues.

5.6 Other reporting requirements

5.6.1 For multi-site studies the CI must inform all PIs of SAEs occurring on the study. It is the responsibility of the CI to communicate all information to the PIs, in particular any information that could adversely affect the safety of participants. This notification must be documented in the SMF. The SAE reports sent to Investigators will be blinded by the CI.

5.6.2 Reports sent to a PI regarding SAEs from other sites must be reviewed by the PI and acted upon if appropriate. Copies of such reports must be kept in the Investigator Site File.

5.6.3 The CI is responsible for submitting Annual Safety Reports to the REC on the anniversary of the favourable ethical opinion and annually thereafter until the end of the study. http://www.hra.nhs.uk/research-community/during-your-research-project/progress-reporting/.

5.6.4 The CI is responsible for notifying any other persons or bodies specified in the protocol or clinical study agreement (e.g. Data Monitoring Committee) of details relating to SAEs/SUSARS.

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. Research related Adverse Incidents must therefore be reported in accordance with the hosting organisation's own Adverse Incident Reporting Procedure/System.

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 studies taking place in NHS Fife must be reported via DATIX (see NHS Fife Policy GP/I9 – Adverse Events).

5.8 Urgent Safety Measures

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

5.8.2 Urgent safety measures can be implemented immediately.

5.8.3 The CI/PI should contact the Sponsor by phone at this time and the REC should be notified in writing in the form of a Substantial Amendment within three days.

5.9 Notification to NHS Fife R&D of SUSARs for 'hosted' studies

Where NHS Fife is hosting a research study, the research team should follow the Sponsor's instructions for reporting SAEs. However, where an SAE is considered to be a SUSAR then the PI 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.

6. ASSOCIATED DOCUMENTS

SOP06(Fife) - Sponsor Agreement for Research Projects Involving Humans, Their Tissue and/or Data
Doc Ref 31-01 - Adverse Event Recording Template
Doc Ref 31-02 - AE&SAE Log
Doc Ref 31-03 - SAE/SUSAR Initial Report Form
Doc Ref 31-04 - SAE&SUSAR Follow-up
NHS Fife Policy GP/I9 – Adverse Events.

7. ABBREVIATIONS

AE	Adverse Event
AI	Adverse Incident
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISF	Investigator Site File
PI	Principal Investigator
REC	Research Ethics Committee
R&D	Research & Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
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.*

Annual Safety Reports to the REC
http://www.hra.nhs.uk/research-community/during-your-research-project/progress-reporting/.

NRES SAE Reporting Form for non-CTIMPs
http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

9. DOCUMENT HISTORY

Version Number:	Edited by (job title):	Effective Date:	Details of Revisions Made:
1.0	Julie Aitken R&D Trials Facilitator	02/02/2015	New
2.0	Julie Aitken R&D Trials Facilitator		Format updated in line with revised SOP template. Further information regarding responsibilities added and text updated to provide clarity and reflect current practice. Associated documents updated to reflect current practice.

10. APPROVAL

APPROVED BY	Date
Professor Alex Baldacchino, Research & Development Director, NHS Fife Signature: 	4th Oct 2018