IDENTIFYING, RECORDING AND REPORTING ADVERSE EVENTS AND URGENT SAFETY MEASURES IN RESEARCH

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1 INTRODUCTION

1.1 Research, Innovation and Enterprise (RIE) oversees the process of research within Edinburgh Napier University (ENU).

1.2 Adverse Event (AE) and other safety event identification, recording and reporting procedures will comply with the requirements of Good Clinical Practice (GCP) – See NIHR guidance on GCP https://www.nihr.ac.uk/health-and-care-professionals/learning-and-support/good-clinical-practice.htm

1.3 Where ENU agrees to co-sponsor a study with another organisation the responsibility for AE reporting must be agreed between both organisations before the study commences and should be clearly documented in an agreement or equivalent.

2 PURPOSE

2.1 To describe the procedure for identifying, recording and reporting AEs and urgent safety measures (USMs) occurring in research projects that are sponsored by ENU.

3 SCOPE

3.1 This Standard operating procedure (SOP) applies to researchers participating in studies sponsored by ENU. This includes non-CTIMPS and some non-clinical psychology and sports projects which may result in distress to participants or adverse events. This SOP is also applicable to RIE members of staff responsible for safety reporting.

4 DEFINITIONS

4.1 **Chief Investigator (CI):** An individual who is responsible for the conduct of the whole project.

4.2 **Principal Investigator (PI):** An individual who is responsible for the conduct of the research at the research site. For multi-site studies there should be one Principal Investigator for each research site. In a single-site study, the Chief Investigator and the Principal Investigator will usually be the same person. If the Principal Investigator is a student in a single-site study their supervisor may be the CI.

4.3 **Study team:** The group of researchers working on the project. This includes all members, including the PI and CI.

4.4 **Non-CTIMP**: Trials that do not involve an Investigational Medicinal Product (IMP) as defined by the MHRA, and therefore do not fall within the scope of the Medicines for Human Use (Clinical Trials) Regulations 2004.

4.5 **Adverse Event (AE):** Any untoward medical (physical and/or psychological) occurrence in a study participant which does not necessarily have a causal relationship with the study intervention.

4.6 **Adverse Reaction (AR):** Any untoward and unintended response/consequence that has occurred due to the intervention.

4.7 **Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR):** Any AE or AR that: results in death of the study participant; is life-threatening*; requires inpatient hospitalisation or extension of an existing inpatient hospitalisation*; results in persistent or significant disability or incapacity; consists of a congenital anomaly or birth defect; results in any other significant medical event not meeting the criteria above

> *Life-threatening in the definition of an SAE or SAR 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/enrolment in the study will not meet SAE criteria. Any hospitalisation that is planned post randomisation, will meet the SAE criteria. The SAE criteria will be met where, in the opinion of the CI the event was 'related' to the research (resulted from the administration of any research procedures), and 'unexpected' in relation to those procedures.

4.8 **Serious Unexpected Serious Adverse Reaction** (**SUSAR):** An unexpected adverse reaction (**UAR**) not consistent with the product information that at any dose: results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect.

4.9 **Recording:** Documenting information of all AEs, ARs, SAEs, SARs, and SUSARs. A record of all events and reactions will need to be kept following the guidelines below.

4.10 **Reporting:** Information regarding SAEs will need to be communicated to RIE using the outlined information and appendices below. If appropriate RIE will then communicate this information to the NHS REC and University integrity committees that gave the favourable opinion of the research within 15 days.

4.11 IRAS Sponsor: Person in RIE who is the research sponsor for the study and manages IRAS applications.

5 RESPONSIBILITIES

5.1 The Chief/Principal Investigator will be responsible for identifying and reporting AEs and other safety events as detailed in this procedure. PIs at the University working in multi-site studies should confirm prior to the study taking place whether they will be required to leave on reporting adverse events, or whether this will be undertaken by the Chief Investigator. In the case of student research, the Director of Studies (DoS) or Lead Academic Supervisor will be considered the Chief Investigator and therefore responsible.

5.2 RIE will be responsible for AE reporting to the NHS REC for ENU-sponsored non-CTIMP studies.. The report should be sent to the NHS Research Ethics Committee that gave the favourable opinion of the research within 15 days of the CI becoming aware of the event. This responsibility may not be delegated to the Investigator.

For non-clinical studies the report should go to the School and University Integrity committees which provided a favourable opinion of the research within 15 days of the CI becoming aware of the event.

6 PROCEDURE

6.1 Identifying and Recording AEs

6.1.1 The decision on what AE data to record will be the result of an assessment of the risk associated with the study before the study is undertaken. **There is no requirement for recording of AE data for non-interventional, non-invasive studies (i.e. questionnaire-based & qualitative studies).** However, you may want informally record this and take suitable actions to mitigate this.

6.1.2 For interventional studies, the study protocol will define: what AEs are not to be recorded, notified and/or reported; and when AEs will be identified. Information in the **Adverse Events Flowchart (Appendix 4)** should be used to identify AEs.

6.1.3 SAE data will be recorded by the Chief/Principal Investigator(s) (or a member of the research team with delegated responsibility to do so) on the **SAE Report Form (Appendix 1: SAE001**). Investigators will record all AEs in the **non-CTIMP AE log (Appendix 2: AELOG001)**, unless otherwise defined in the protocol. AE details will be entered into the AE log as soon as possible after being informed of the event. The log will be held in a safe and confidential form and location by the Principal Investigator.

6.1.4 AEs and SAEs should be recorded from the time the participant signs the consent form to take part in the study, unless otherwise defined in the protocol.

6.1.5 AEs and SAEs will be followed up until outcome of the study participant is determined by the relevant healthcare professional (e.g. recovered, recovered with sequelae, or death), unless otherwise defined in the protocol. The CI/PI should seek ongoing information regarding the study participant and report it to RIE to be recorded as sponsor.

6.1.6 AEs or SAEs may also be identified by affiliated support services or departments, for example, toxicology, social services, General Practitioners, student counselling. Where notification of untoward events or occurrences would not occur as standard practice, the procedure for notifying the Principal Investigator of such adverse events must be clearly documented in the protocol or study specific procedures (e.g., described in ethics application, contract agreements with site management organisations). If RIE is notified directly, the CI/PI will be informed and the relevant paperwork should be completed.

6.2 Assessment of AEs

6.2.1 Each AE must be assessed for seriousness, causality, severity and expectedness by the Chief/Principal Investigator or another suitably qualified healthcare practitioner in the research team who is trained in recording and reporting AEs and who has been delegated this role. During CI/PI absences appropriately qualified, experienced and trained site staff may assess causality and report SAEs if they have been delegated this responsibility and this has been recorded appropriately by the CI/PI.

6.2.2 For randomised double-blind studies, AEs will be assessed as though the study participant was randomised to the study intervention.

6.2.3 All AEs should be referred to RIE as sponsor to assist in determining their seriousness, causality, expectedness, and severity.

6.3 Assessment of Seriousness

6.3.1 The Principal Investigator will make an assessment of seriousness (as defined in section 4).

6.4 Assessment of Causality

6.4.1 The Chief/Principal Investigator will make an assessment of whether the AE is likely to be related to the study intervention according to the following definitions: Unrelated: where an event is not considered to have occurred as a result of the study intervention. Possibly Related: The nature of the event, the underlying physical/psychological condition, or temporal relationship make it possible that the AE has a causal relationship to the study intervention.

6.4.2 Where there are two assessments of causality (e.g. between Principal Investigator and Chief Investigator when they are not the same person), the causality assessment by the Principal Investigator cannot be downgraded. In the case of a difference of opinion, both assessments are recorded and the 'worst case' assessment is used for reporting purposes.

6.5 Assessment of Expectedness

6.5.1 If the AE is judged to be related to the study intervention, the Chief/Principal Investigator will make an assessment of expectedness. Expected: The type of event is expected in line with the study intervention. Unexpected: The type of event was not listed in the protocol or related documents/literature as an expected occurrence/outcome.

6.6 Assessment of Severity

6.6.1 The Chief/Principal Investigator will make an assessment of severity for each AE and this should be recorded on the AE or SAE form according to the following categories: Mild: an event that is easily tolerated by the study participant, 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.

6.6.2 The term 'severe' used to describe the intensity of an event should not be confused with the term 'serious', as defined in section 4, 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.

6.7 Information regarding AEs and SAEs to be collected

6.7.1 AEs and SAEs must be reported to RIE within 24 hours of the CI/PI having become aware of their existence. This should include an up to date copy of the non-CTIMP AE log (Appendix 2: AELOG001), including the current event, and the SAE Report Form (Appendix 1: SAE001) if the CI/PI has deemed the adverse event serious. If the CI/PI is unsure of severity, they should submit a copy of the non-CTIMP AE log (Appendix 2: AELOG001) to RIE with detail of the current event and ask for support in clarifying. Where this report comes from an affiliated support service or department, RIE will inform the CI/PI and ask them to complete the relevant paperwork. RIE will record all adverse events and related information on an internal database.6.7.2 If any of the required information is not available at the time of reporting, the Chief/Principal Investigator must ensure that any missing information is reported to RIE as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event (see section 6.8 for reporting to RIE).

6.7.3 Where missing information has not been sent to RIE after an initial report, RIE will contact the Chief Investigator and request the missing information. If it is not possible to supply any further detail, this will be recorded on the database.

6.7.4 If reports are received by RIE with personal identifiable data, the identifiable data will immediately be deleted by RIE and the sender informed of this breach in confidentiality/data protection and that they must take steps to ensure that this does not reoccur, where appropriate.

*Template (**Appendix 3: Adverse Event Flowchart - Identifying**) illustrates the reporting procedure and can be used by investigators to clarify AE reporting requirements.

6.8 Reporting SAEs to the Sponsor (delegated person in RIE)

6.8.1 All AEs and SAEs should be reported to RIE as sponsor.

6.8.2 The Investigator is responsible for reporting SAEs to RIE within 24 hours of becoming aware of the event.

6.8.3 AEs should be reported via an up-to-date copy of the non-CTIMP AE log (Appendix 2: AELOG001), including the current event, being sent to RIE. SAEs should be reported via the aforementioned logbook, a completed SAE Report Form (Appendix 1: SAE001),. All documents will be emailed as a .pdf file to researchintegrity@napier.ac.uk. SAE reports will be completed as far as possible and will be signed and dated by the Investigator.

6.8.4 SAE reporting to RIE should maintain the blind (participant anonymity) unless it is considered necessary to break the blind in the interest of study participant safety.

6.8.5 The IRAS Sponsor in RIE or designee will review the reported event and provide guidance to the reporter if needed. If deemed an AE, they will notify the CI/PI, and record the event within 96 hours. If deemed an SAE and in receipt of a completed SAE form, the IRAS Sponsor or designee will send an email to confirm receipt of the SAE report within 96 hours. If this email is not received within 96 hours of sending the report to RIE, the Investigator must telephone RIE on 01314556302 to check that the report has been received by RIE.

6.8.6 When a potential SAE has been reported, the Convenor of the University Research Integrity Committee may form a panel to help determine if an SAE has occurred as per the definitions in this policy. The panel would usually include the following roles:

Convenor University Research Integrity
IRAS Sponsor
School Research Integrity Lead
Lead Principal Investigator

The panel would review all relevant information presented by the Lead Principal Investigator to make a determination if a SAE has occurred. If this is the case, the SAE would be reported as per the procedures in this policy

6.8.7 Once an AE notification or SAE report is received by RIE it will be entered onto the RIE Adverse Events/Serious Adverse Events database by the IRAS Sponsor or designee. RIE will notify the appropriate school research ethics committee convenor of the adverse event. If deemed serious, RIE will also notify the school Director of Research to provide support, and the school Director of Research will notify the line manager of the CI/PI.

6.8.8 All copies of SAE reports emailed to RIE and any follow-up information and correspondence will be kept by the Investigator in the Investigator Site File (ISF) and by the Sponsor in the Sponsor File (non-CTIMP File Master).

6.8.9 For multicentre studies, RIE will report SAEs, as required, to the Chief Investigator within agreed timelines.

> *Template (**Appendix 4: Adverse Event Flowchart - Reporting**) illustrates the reporting procedure and can be used by investigators to clarify AE reporting requirements.

6.9 Expedited Reporting of Related and Unexpected SAEs to NHS Research Ethics Committee(s)

6.9.1 RIE is responsible for reporting SAEs that are considered to be 'possibly related' and 'unexpected' to the NHS Research Ethics Committee (REC) within 15 days of becoming aware of the event. A copy of the report should also be sent to the relevant School Research Integrity Committee (SRIC).

6.9.2 Related and unexpected SAEs from double-blinded studies will be unblinded after informing RIE but before reporting to the NHS REC.

6.9.3 Related and unexpected SAEs reported for participants not receiving the study intervention WILL NOT be reported to the NHS REC. The study team WILL NOT be informed of the unblinding result.

6.9.4 In order to maintain the blind, the study team will be informed that reporting procedures were followed by RIO and results reported where necessary to the NHS REC/SRIC.

6.9.5 Related and unexpected SAE reports will be sent to the NHS REC with the Health Research Authority (HRA) Safety Report Form. Any relevant follow-up information will be submitted to the NHS REC as appropriate.

6.9.6 Line listings, unless stated in the study's DM[E]C Charter, will be reported by the PI/CI to the Data Monitoring (and Ethics) Committee (DM[E]C) and/or the Trial Management Group (TMG) and/or the Study Steering Committee (SSC) as appropriate.

6.9.7 In multicentre research studies, it is also the responsibility of the CI to inform the PIs at each site of all SAEs reported.

6.10 Urgent Safety Measures

6.10.1 If a safety issue is identified during a study, investigators must act immediately to protect participants from any immediate threat to their health and safety. Investigators may implement a deviation from or change to the protocol to eliminate an immediate hazard to study participants without prior approval from the NHS REC/SRIO. This is defined as an urgent safety measure (USM).

6.10.2 The Chief Investigator must then notify the NHS REC/SRIC and RIE in writing within 3 days of the incident. Written notification is in the form of a substantial amendment to the NHS REC and Sponsor/SRIC.

6.10.3 Notification of a USM should be delivered by email to RIE at researchintegrity@napier.ac.uk marked 'urgent safety measure'; and by email to the relevant NHS REC/SRIC, marked 'urgent safety measure'; and by email to the relevant NHS R&D offices, marked 'urgent safety measure'.

6.10.4 A copy of the notification and receipt must be filed in the Study Site File and in the Sponsor File (non-CTIMP File Master).

6.10.5 The RIE Health Research Governance Manager, or designee, will ensure the information is forwarded to the sponsor to assess if the risk/benefit balance of the study has been altered and if it is appropriate for ENU to continue as the sponsor.

7 REFERENCES AND RELATED DOCUMENTS

International Council for Harmonisation - Good Clinical Practice E6 Guidelines.
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
Serious Adverse Event Report Form (non-CTIMP)
Adverse Event Flowchart – Identifying
Adverse Event Flowchart – Reporting
AE Log (non-CTIMP) AELOG01
Cover Sheet and Return Receipt SAE001C

8 DOCUMENT HISTORY

Version number	Date	Reason for change
4	23/7/2021	Update to make definition of non-CTIMP clearer and add other types of research which could result in AEs. Also update name change RIO to RIE.

9 APPROVALS

Signatures	Date
Author: Name: Signature:	
Sponsor: Name: Signature:	
Chair of University Research Ethics Committee: Name: Signature:	

Appendix 1 SAE001

SERIOUS ADVERSE EVENT (SAE) FORM (non-CTIMP)

**** DO NOT SEND PARTICIPANT IDENTIFIABLE DATA WITH THIS FORM ****

FORMS MUST BE SENT TO RIE WITHIN 24 HOURS OF

THE SITE RESEARCH TEAM BECOMING AWARE OF THE SAE

Study name:	**Sponsor number (if applicable): AC**_ _ _ _ _
Participant ID code/no :	**Date of report** *(dd/mm/yyyy)***:**
Centre name:	**Centre no:** _ __ _ _

- This form is for all studies **except** clinical trials of investigational medicinal products or clinical investigations of medical devices.
- Complete the form as far as possible, and email to RIE (researchintegrity@napier.ac.uk).
- The Chief Investigator should retain the form once completed. Additional 'Follow-up' and 'final' information can be added at a later date and the form should be re-scanned and emailed to RIE after additional information has been added.

TO BE COMPLETED BY RIE (*INTERNAL USE ONLY*)	
Date and time received by RIE system: DD/MM/YYYY	HH:MM:
Date acknowledged by RIE: DD/MM/YYYY	Initials:

1. DETAILS OF REPORT:

Date PI first aware of SAE *(dd/mm/yyyy)* : _ _ / _ _ / _ _ _ _		
Report status *(tick all that apply)* :	Initial ☐ Interim follow-up ☐ Final follow-up ☐	**Date submitted** (dd/mm/yyyy)**:**

2. CIRCUMSTANCES OF EVENT:

Date of SAE onset *(dd/mm/yyyy)* : _ _ / _ _ / _ _ _ _
Diagnosis:

Describe the circumstances of the event including action taken *(maximum 1000 characters):*
What is your assessment of the implications, if any, for the safety of study participants, and how will these be addressed?

3. SERIOUSNESS *(please categorise this event, ticking <u>all</u> appropriate options)**:***

Death ☐	Life threatening ☐	Inpatient hospitalisation or prolongation of existing inpatient hospitalisation ☐
Persistent or significant disability or incapacity ☐	Congenital anomaly or birth defect ☐	Other medically important event ☐ Specify:

4. ASSESSMENT OF EVENT *(event must be assessed by the Principal Investigator or a suitably qualified clinician listed on the study delegation log)**:***

<u>(i) Causality</u>:

(a) Is it reasonably possible that the event was related to taking part in the study? Possibly related ☐ Unrelated ☐

(b) If possibly related, please state your reason(s):

(ii) Expectedness: *(only to be completed if SAE is causally related to the treatment allocation)* **:**	
Indicate whether this event was:	Expected ☐ Unexpected ☐
Indicate participant's treatment allocation if not blinded *(if blinded, assume participant received intervention)*	Control / Standard care ☐ Intervention ☐ Specify Intervention (or state 'blinded'):
(iii) Severity:	Mild ☐ Moderate ☐ Severe ☐
(iv) Date of assessment: *(dd/mm/yyyy)* **:**	_ _ / _ _ / _ _ _ _

5. OUTCOME OF EVENT:

☐ Completely recovered Date recovered *(dd/mm/yyyy)*: _ _ / _ _ / _ _ _ _ *Please initial and date entry here:* XXX D D / M M / Y Y Y Y	☐ Condition deteriorated *Please initial and date entry here:* XXX D D / M M / Y Y Y Y	☐ Death Date of death *(dd/mm/yyyy)*: _ _ / _ _ / _ _ _ _ Post mortem? Yes ☐ No ☐ *Please initial and date entry here:* XXX D D / M M / Y Y Y Y
☐ Condition still present and unchanged *Please initial and date entry here:* XXX D D / M M / Y Y Y Y	☐ Condition improving *Please initial and date entry here:* XXX D D / M M / Y Y Y Y	

6. DECLARATION FOR INITIAL REPORT:

Name of Person completing initial report : Address: Phone: Email:
ALL REPORTS MUST BE SIGNED AND DATED BY THE PRINCIPAL INVESTIGATOR (or a suitably qualified clinician listed on the study delegation log).
PI or designee name:
PI or designee signature: Date: _ _ / _ _ / _ _ _ _ *(dd/mm/yyyy)*

7. DECLARATION FOR FINAL FOLLOW UP REPORT:

Name of Person completing follow up report : Address: Phone: Email:
ALL REPORTS MUST BE SIGNED AND DATED BY THE PRINCIPAL INVESTIGATOR (or a suitably qualified clinician listed on the study delegation log).
PI or designee name:
PI or designee signature: Date: _ _ / _ _ / _ _ _ _ *(dd/mm/yyyy)*

APPENDIX 2: Adverse Events Log (AELOG01)

Participant Unique Identifier Code:

Study Title	Study Ref #	Site Location	Principal Investigator

Adverse event	Start date	SAE* 1.Yes (also complete SAE form) 2. No	Causality 1. Unrelated 2. Possibly Related	Severity 1. Mild 2. Moderate 3. Severe	Expectedness 1. Expected 2. Unexpected	DATE of assessment and INITIALS of delegated reporter	Outcome 1. Resolved 2. Ongoing	Date Resolved	AE Recorded by (initials)

A serious adverse event is one that (i) results in death, (ii) is life threatening, (iii) requires hospitalisation or extension of existing hospitalisation, (iv) results in persistent or significant disability or incapacity or (v) consists of a congenital anomaly or birth defect (vi) other medically significant event.

Notes

See SOP procedure for reporting AEs and SAEs.

The Adverse Event Log should be used as a template for adverse event (AE) data collection in studies. This data set is the minimum that should be collected and should not be altered without the sponsor's prior agreement.

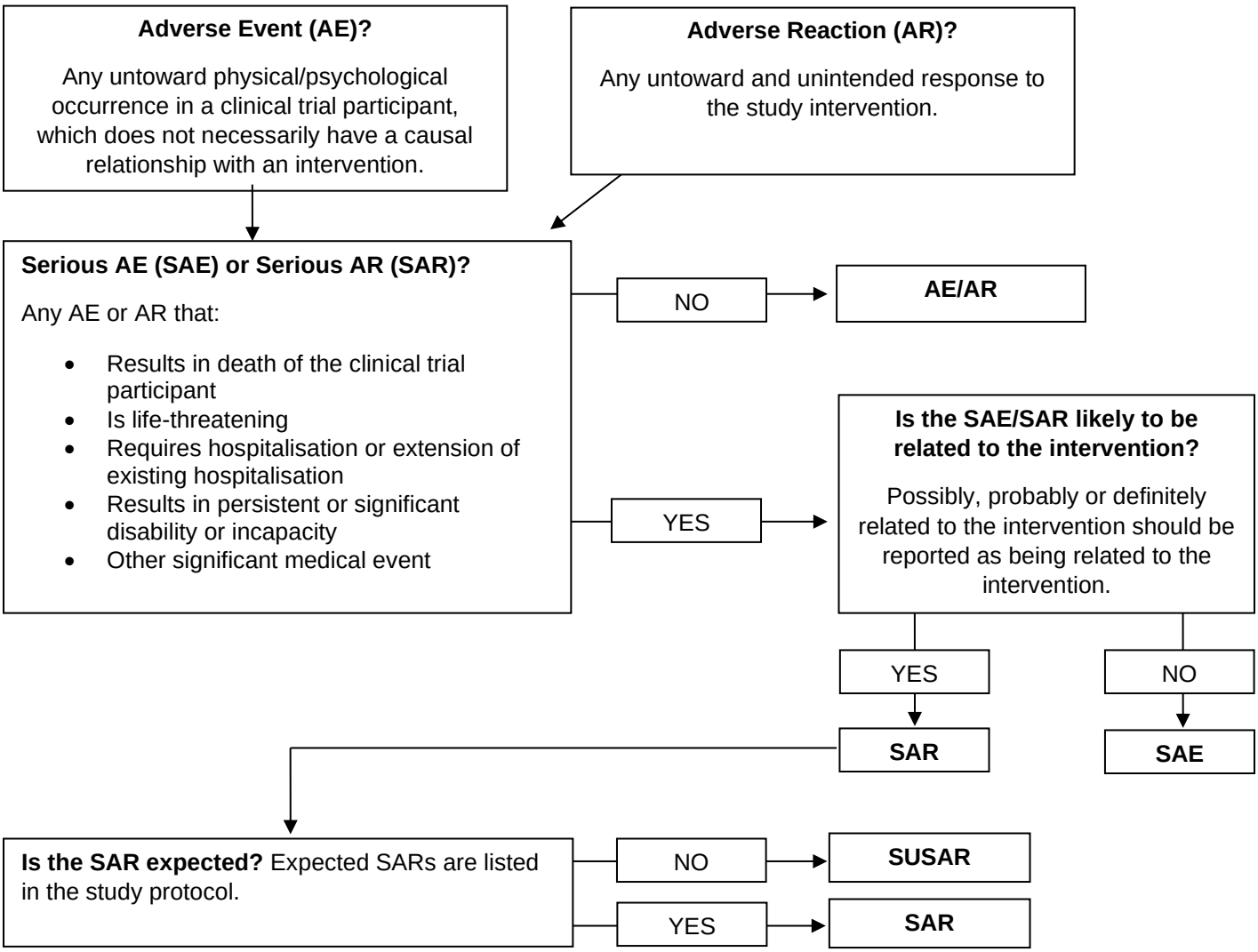
Certain types of study will require additional data to be collected – for example, studies involving Clinical Investigations of Medical Devices (CIMDs) must also collect data on Adverse Device Effects (ADEs).

Additional information relevant to each particular study may also be collected if appropriate.

Guidance

1) Ensure members of the research team have initialled the delegation or signature log so individuals initialling the AE log can be identified. If only a signature is collected on the delegation/signature log then the clinician/delegated person must sign the AE form rather than just initial it.
2) AE logs should include the participant unique identifier code number only (i.e. no personal identifiable information).
3) Date Resolved: where appropriate, the protocol should clearly identify the time period each adverse event should be followed up.

APPENDIX 3: Adverse Event Flowchart – Identifying



APPENDIX 4: ADVERSE EVENT FLOWCHART – REPORTING