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SOP 207
Adverse Events: Identifying, Recording and Reporting Adverse Events for Device Trials sponsored by NNUH

For Use in:	Research
By:	All staff
For:	All staff involved in the conduct of health care research
Division responsible for document:	Research & Development
Key words:	Adverse Events, Device Studies
Name of document author:	Basia Brown
Job title of document author:	Research Governance Coordinator
Name of document author's Line Manager:	Julie Dawson
Job title of author's Line Manager:	Research Services Manager
Supported by:	Julie Dawson NNUH Sarah Ruthven UEA
Assessed and approved by:	Julie Dawson: Research Services Manager NNUH Sarah Ruthven: Research Manager UEA
Date of approval:	07.12.2023
To be reviewed before: This document remains current after this date but will be under review	07.12.2026
Reference and / or Trust Docs ID No:	16878
Version No:	3

Version and Document Control:

Version No:	Date of update	QPulse Change Request ref: (CR no.)	Change Description	Author
2	07.12.2023	CR130	Deleted reference to transitional arrangements for placing CE device on UK market. Moved definitions to appendix. Updated reporting requirements to MHRA Clarified R&D responsibility to report via MORE. Deleted section relating to old reporting process.	Basia Brown, UEA, NCTU

This Standard Operating Procedure (SOP) is available on the Research & Development pages on the NNUH website
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1. Contents

2. Definitions of Terms Used / Glossary

AE	Adverse Event
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
CE	Conformitè Europëenne mark – mandatory conformity marking for goods sold in the European Economic Area (EEA)
CI	Chief Investigator
CIP	Clinical Investigation Plan
CRF	Case Report Form
IB	Investigator's Brochure
NCTU	Norwich Clinical Trials Unit
NNUH	Norfolk and Norwich University Hospital
PI	Principal Investigator
R&D	Research and Development
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UEA	University of East Anglia
UKCA	UK Conformity Assessed marking – mandatory marking used for products being place on the market in Great Britain
USADE	Unanticipated Serious Adverse Device Effect

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3. Scope

The aim of this SOP is to describe the process for identifying, recording and reporting of adverse events for device trials involving non-CE / UKCA marked devices or CE / UKCA marked devices that are being used outside their intended use(s) covered by the CE / UKCA marking that require MHRA approval, and are sponsored by NNUH

4. Introduction

This SOP applies to all device trials, sponsored by the NNUH, involving non-UKCA/ /CE marked devices or UKCA/CE marked devices that have been modified or are to be used for a new purpose.

With prior agreement with the sponsor, the process may be modified to meet the needs of individual studies.

It is essential that all adverse events which occur during the course of a study are recorded and reported appropriately, in order to ensure that patient safety is maintained.

In order to comply with the appropriate legislation, all researchers must be aware of the definitions (see appendix 3) and procedures in relation to AEs; for medical device studies this legislation includes:

- The Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK MDR 2002)
- Part IV of the UK Medical Devices Regulations 2022 – relating to in vitro diagnostic devices

5. Purpose

To ensure that patient safety is maintained, adverse events are reportable from the time of participant study enrolment unless study specific exclusions are detailed in the device trial clinical investigation plan (CIP).

6. Rules

Failure to report incidents, or deal with incidents adequately, can result in study suspension, regulatory approval being withdrawn from an individual project, or, in extreme cases, from all research conducted by an individual investigator.

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7. Responsibilities

CI / PI

The Chief Investigator (CI) has overall responsibility for the conduct of the study.

The Chief Investigator (CI) /Principal Investigator (PI) must be aware of the NNUH systems for reporting adverse events by complying with this SOP.

All device trials must have a sponsor legally responsible for the conduct and monitoring of the trial. The Research & Development (R&D) Office will be responsible for ensuring monitoring is conducted for all device trials for which the Trust acts as Sponsor.

It is the responsibility of the local PI to ensure that study specific SOPs can be operated without conflict with this SOP and in accordance with all organisational polices related to research.

Norwich Clinical Trials Unit (NCTU)

- Where NCTU has been delegated the sponsor activities, NCTU forms and reporting procedures instructions may be followed as described in study documentation, providing that they are not in breach of this SOP.
- If the NCTU is delegated the management of a trial, NNUH may delegate the safety reporting responsibilities to the CTU trial manager. This decision will be documented in the protocol, NNUH and UEA sponsorship agreement or clinical trial agreement.
- NCTU will form a Trial Management Group to support the review of SAE / SUSAR report forms for trials where CTU have been delegated the safety reporting responsibilities.
- When safety reporting is managed by the Clinical Trials Unit, copies of SAEs for NNUH sponsored studies need to be provided to the R&D office (rdsae@nnuh.nhs.uk) to ensure review by Joint Research Governance Committee.

8. Identification and recording of Adverse Events

The PI at site or designee is responsible for the identification of any AE or ADE as defined in the CIP.

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Procedure for the assessment and reporting of Adverse Events

- In the event of an AE the investigator or delegate member of the research team should review all documentation (e.g. hospital notes and diagnostic reports) relevant to the event
- An assessment of seriousness, severity, causality and expectedness must be made

- All AEs should be recorded for all trial subjects from the time of their enrolment into the study.
- The event and relevant comments should be recorded in the subject's medical notes and source data

- Except where the CIP states otherwise, all AEs that are not considered serious should be recorded in detail in the CRF or equivalent to allow analysis at a later stage

- AEs identified in the CIP as critical to the evaluations of the safety of the study shall be reported to the sponsor in accordance with the reporting requirements documented in the CIP.

- There are no requirements to report these events to the Sponsor or Regulatory Agencies unless the AE meets the criteria of a SAE/SADE.
- All AEs must be observed to ensure that they do not escalate to an SAE/SADE.

- If considered serious, unexpected and related to the event then it will be subject to expedited reporting as a potential USADE
  - See Appendix 2 for assessment process
  - Refer to SOP 230 for Urgent Safety Measures

- At the conclusion of the study all AEs occurring during a study will be subject to statistical analysis and subsequent conclusions must be included in the final study report

9. Reportable Events

9.1 Reporting to Sponsor

All SAEs / SADEs /USADEs in studies sponsored by NNUH must be reported to the Sponsor **within 24 hours** of the research team becoming aware of the event unless they are listed in the CIP as expected events.

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- The Investigator or delegated member of the research team will complete the NNUH SAE Device Trial report form (Appendix 1 - Trust Docs ID: 17471). The initial report will include as much information as is available at the time.
- The report should be emailed to rdsae@nnuh.nhs.uk – the CI must be copied in or directly informed.
- R&D will send an acknowledgment of receipt of the report form to the sender by noon of the following working day. If acknowledgment of the report form is not received it is the responsibility of the investigator or delegated member of the research team to contact R&D immediately.
- Missing information will be provided by the Investigator within a maximum of 7 working days of the initial report being sent to R&D.

9.2 Follow on Reporting

After submitting the initial report the investigator is required to actively follow up the subject until either:

a) The SAE resolves, or
b) The sponsor and CI/PI agree that no further follow-up required*.

*This decision must be documented in the TMF. It will be the CIs decision as to how long the SAE will be followed up for. Investigators (or delegated persons) will provide follow-up information each time new information is available - a follow up report should be submitted. The report will be completed and emailed to the CI and rdsae@nnuh.nhs.uk.

The Research Governance Administrator or delegate will collate updates and any follow up report from the Investigator/trial manager.

When safety reporting is managed by a clinical trials unit copies of SAEs for NNUH sponsored studies need to be provided to the R&D office (rdsae@nnuh.nhs.uk) to ensure review by Joint Research Governance Committee.

9.3 Procedure for Multi-centre Studies

The responsibility for this evaluation can be shared between the CI and PIs and this must be stated in the delegation of responsibilities between the Sponsor, CI, and PI. It may be most appropriate for the treating PI at each local site to evaluate each event, before reporting it to the CI. It must be stated in the CIP who will take responsibility for the assessment and reporting of such events to the Sponsor and CI simultaneously.

This SOP assumes that responsibility of initial assessment and reporting to the CI lies with the PI.

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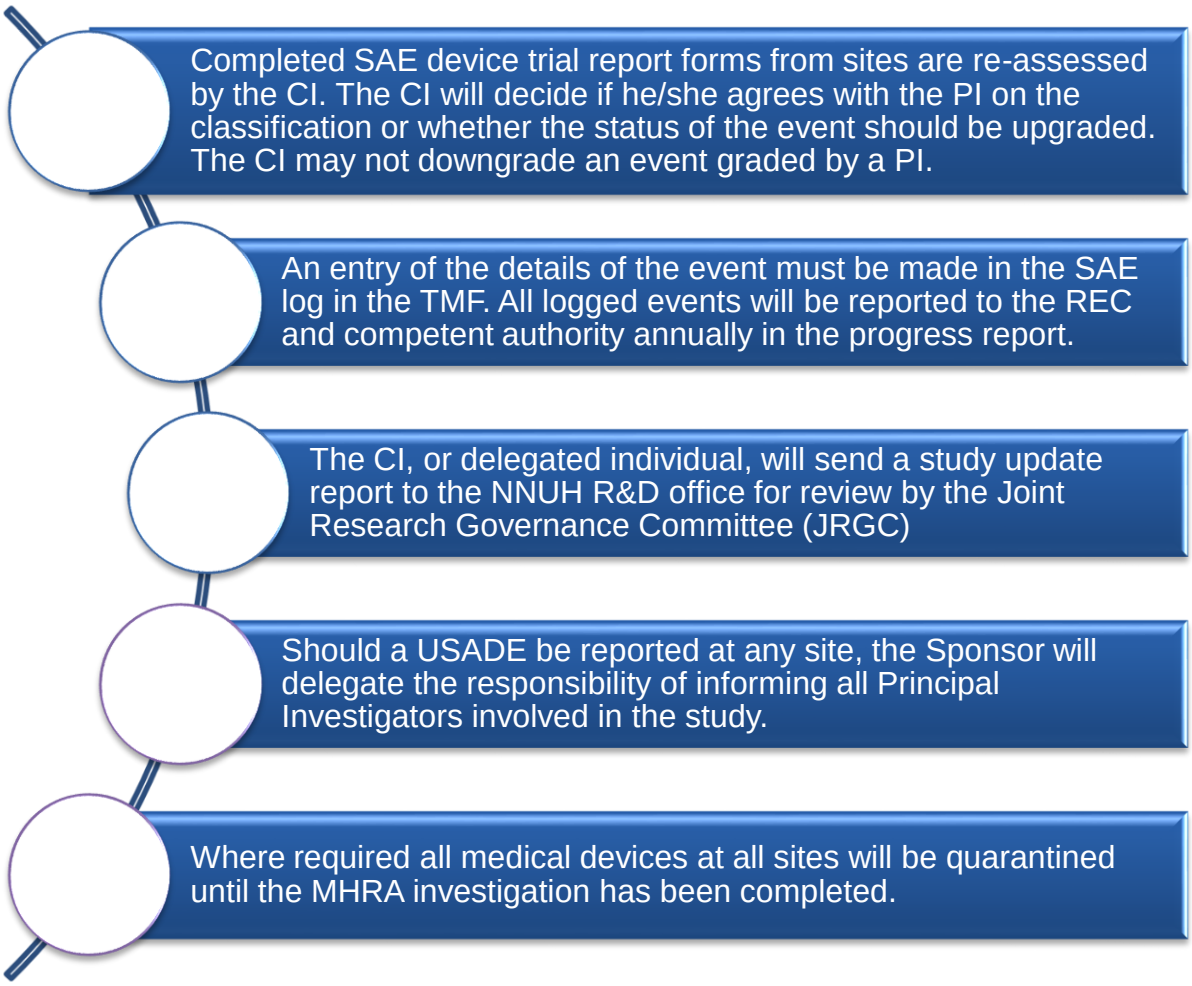

9.4 Reporting to MHRA

The following events are considered reportable:

- Any serious adverse event
- Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
- Any new findings in relation to any event referred to in the above two points.

All SAEs and device deficiencies, whether initially considered to be device/procedure related or not, involving a device under clinical investigation within Great Britain should be reported to the MHRA as per timelines specified below. The submission should be via MHRA reporting portal MORE. It will be responsibility of the R&D department to report them after being notified. (R&D WPD 004 processing of Adverse Events Reports provides information on how to complete a submission on the MORE portal). For all reportable events where there is an imminent risk or death, serious injury or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: the sponsor or designee must report to the MHRA immediately, but no later than **2 calendar days** after they become aware of such an event or new information in relation to an already reported event.

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Any other reportable events outlined above or any new finding/update in relation to them must also be reported immediately, but no later than **7 calendar days** after the sponsor becomes aware of them.

The letter of no objection from the MHRA will also detail whether summary reports (including their frequency) need to be submitted to the MHRA. The letter of no objection will also detail whether protocol deviations must also be reported to the MHRA.

9.5 Reporting to REC

All SAEs which are:

- **related** to the study (ie they resulted from administration of any of the research procedures) and
- **unexpected** (ie not listed in the protocol as an expected occurrence)

should be emailed to the REC using the Non-CTIMP safety report to REC form. These should be sent within 15 days of the chief investigator becoming aware of the event[1].

The CI is also required to include a report of the safety of participants in the annual progress report to the REC. Individual reports will be reviewed by the REC at a subcommittee or committee meeting. Any requests for further information should be provided as applicable and all correspondence should be copied to the Sponsor.

10. Quarantine of Devices

The device must not be returned to the manufacturer until the MHRA has been given the opportunity to carry out/complete an investigation, if required by the MHRA. In addition, the device **should not** be: Discarded; Repaired; Returned to the manufacturer; or removed from the site / organisation premises, without agreement from the Sponsor.

All material evidence i.e. devices/parts removed, replaced or withdrawn from use following an incident, instructions for use, records of use, repair and maintenance records, packaging materials, or other means of batch identification **must** be:

- clearly identified and labelled
- stored securely

Evidence should not be interfered with in any way except for safety reasons or to prevent its loss. Where appropriate, a record should be made of all readings, settings and positions of switches, valves, dials, gauges, and indicators, together with photographic evidence and eyewitness reports.

Consideration should be given to the practicality and implications of quarantining the device; for example if the device is an implantable device all further supplies of the device should be quarantined as a precaution until further advice is sought.

[1] *https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/ - Safety Reporting for non-CTIMP studies (including clinical investigations of medical devices)*

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The Investigator and the Sponsor will undertake any requirements outlined in the MHRA investigation and follow-up as instructed.

11. Non-Compliance

Where evidence of non-compliance is identified **SOP 210 Managing Protocol and Regulatory Non-Compliance including Serious Breaches** will be followed.

12. References and Related Documents

References and Related Documents
ICH GCP E6 / SI 2004/1041
Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK MDR 2002)
Part IV of the UK Medical Devices Regulations 2022 – relating to in vitro diagnostic devices
Procedural Document Development Policy Trust ID 19976
The UK Policy Framework for Health and Social Care Research
SOP 210 Managing Protocol and Regulatory Non-Compliance including Serious Breaches
SOP 230 Urgent Safety Measures
SOP 835 Clinical Data Management System: EMERGENCY UNBLINDING.
WPD 004 processing of Adverse Events Reports

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13. Approval

Author	Basia Brown
Role	Research Governance Coordinator
Approved & Authorised NNUH	Julie Dawson
Role	Research Services Manager
Signature	DocuSigned by: Julie Dawson 4CBAB366CF354A2...
Date	12 December 2023 | 10:23 GMT
Approved & Authorised UEA	Sarah Ruthven
Role	Research Manager
Signature	DocuSigned by: Sarah Ruthven 50D5F3BEE2F04C1...
Date	15 December 2023 | 8:14 GMT

14. Training Implication

Training Implication	**Yes**
Actions required	• Additional training may be required • Matrix to be updated

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Appendix 1 – AE Form for Device Trials

see https://www.nnuh.nhs.uk/research-and-innovation/

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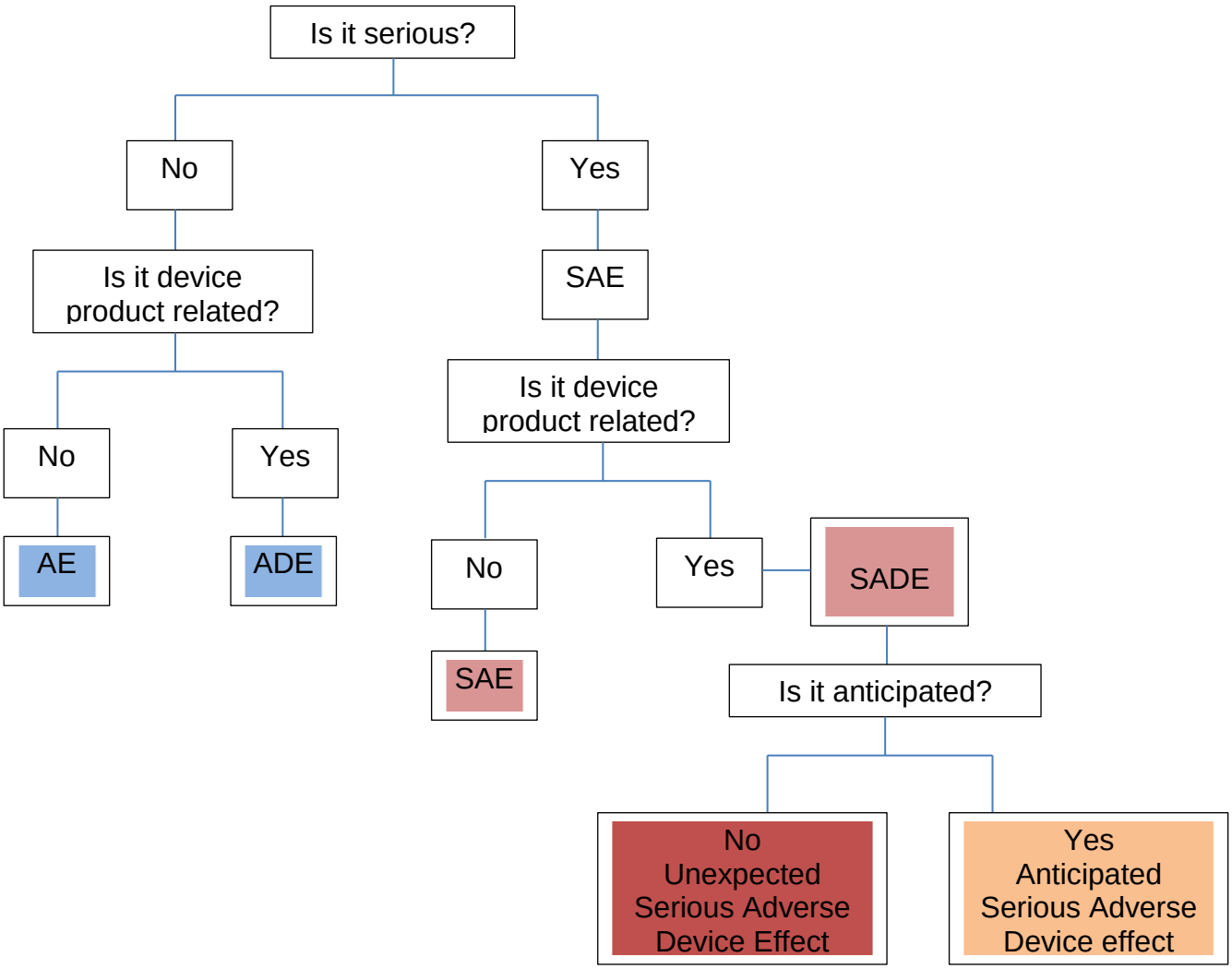
Appendix 2 - AE Assessment Process



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Appendix 3 - Definitions:

Device Deficiency
Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Device Malfunction
Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the CIP.

Clinical Investigation Plan (CIP)
A document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record keeping of the clinical investigation.

Investigator's Brochure (IB)
A compilation of the current clinical and non-clinical information on the investigational medicinal device relevant to the clinical investigation.

Adverse Event (AE)
An adverse event (AE) is an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device/intervention.

Adverse Device Effect (ADE)
An adverse device effect (ADE) is an adverse event that is deemed to be 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 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.

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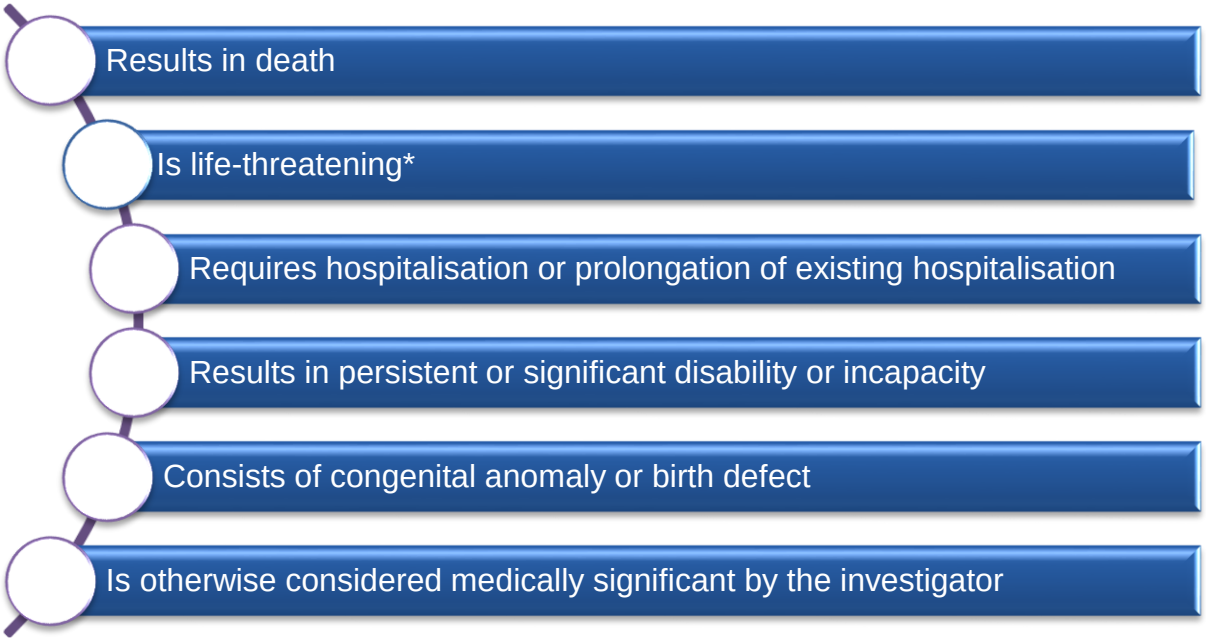
Serious Adverse Event (SAE)
A SAE is defined as any untoward occurrence that



* Life-threatening, in the definition of an SAE or SAR, refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe. Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.
A planned hospitalisation for a pre-existing condition, or a procedure required by the trial protocol, without a serious deterioration in health, is not considered to be a serious adverse event unless specified in the clinical trial protocol.

Serious Adverse Device Effect (SADE)
A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)
A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the CIP or in the risk assessment.

Anticipated Serious Adverse Device Effect (ASADE)
A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the current version of the CIP or in the risk assessment.

Severity
The relationship between the investigational medical device and the impact on the patient's quality of life.

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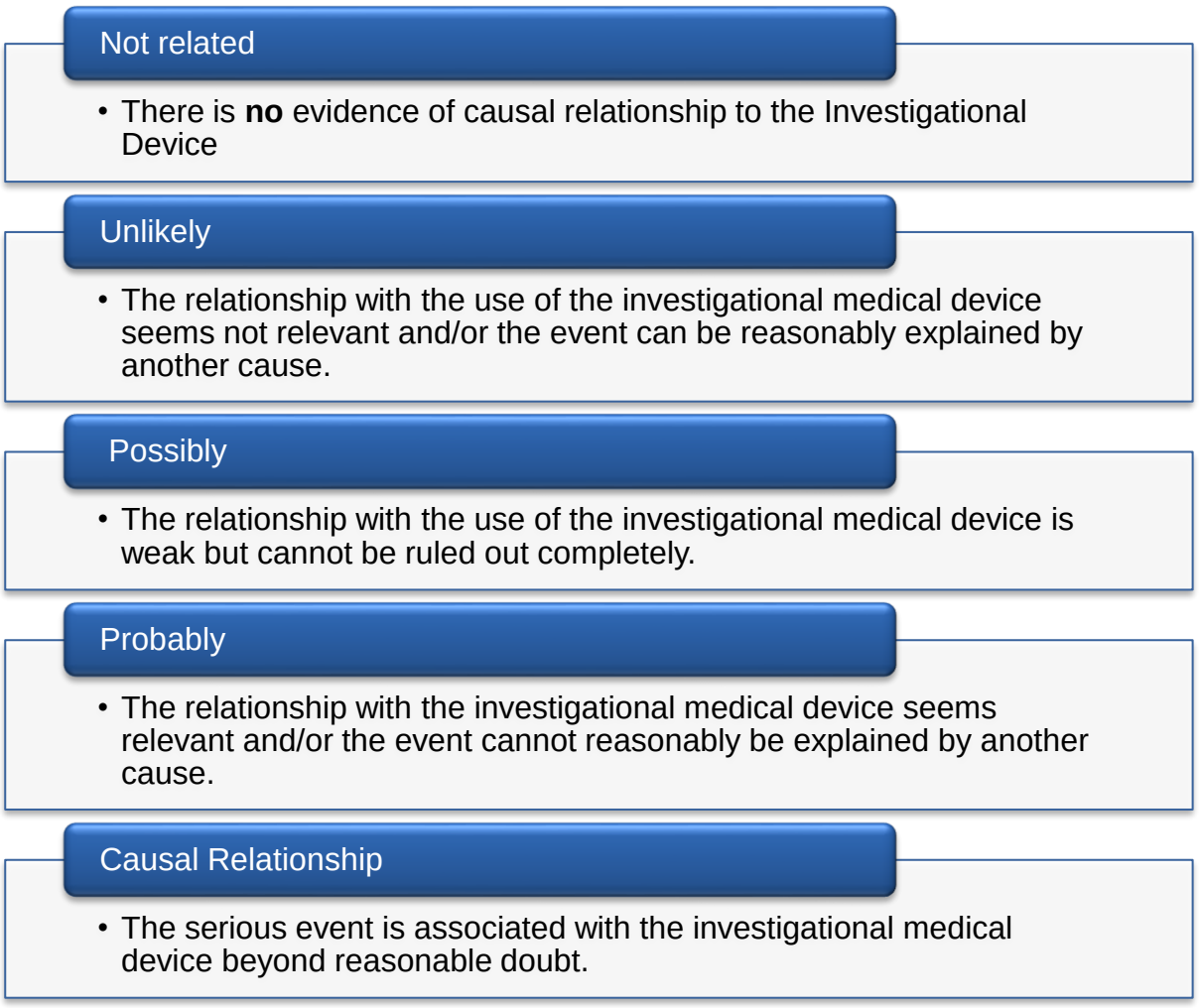
Causality
The relationship between the device and the event.

The investigator will use clinical judgment to determine the relationship, categorisations are as follows:



Expectedness
The assessor must consult the current version of the CIP and/ or IB to determine where an event is expected.

Where applicable in blinded studies, unblinding must occur to assess treatment assignment. For further instruction refer to **SOP 835 Clinical Data Management System: EMERGENCY UNBLINDING.**