Technology, Infrastructure and Environment Directorate Clinical Research Governance Team

Standard Operating Procedure

Safety Reporting for University of Liverpool Sponsored Research

SOP007

Author	**Date of Approval**
Karen Jennings-Wilding	27th April 2026
Approved on behalf of ratifying committee	**Date of Approval**
Professor Tony Marson (Chair of Clinical Research Regulatory Oversight Committee)	27th April 2026

Document Control

Issue Date	27/04/2026
Effective Date	28th April 2026
Review Date	27th April 2028
This document is controlled using Ideagen Quality Management and is made available on the University of Liverpool Clinical Directorate website. The web version of this document is the only version that is maintained. This document is uncontrolled when printed and as such, may not necessarily contain the latest updates and amendments.	

Document History can be viewed on Ideagen Quality Management

Review Process Prior to Sign Off

Name of Committee	**Date**
Joint Research Office Sponsorship Committee – Version 1	7th July 2015
Chair of Joint Research Office Sponsorship Committee – Version 2	27th July 2017
Joint Research Office Sponsorship Committee – Version 3	14th September 2017

Name of Committee	Date
SPARK Sponsorship Committee (Version 4)	16th June 2022
Vice-Chair of Clinical Research Regulatory Oversight Committee (Version 5)	5th August 2024
Clinical Research Regulatory Oversight Committee (Version 6)	23rd April 2026

Contents

1. Introduction 3
2. Scope of Procedure 3
3. Who 4
4. When 4
5. Clinical Trials of Investigations Medicinal Products (CTIMPs) 4
6. Clinical Investigations of Medical Devices (CIMDs) 10
7. Other clinical research 13
8. Roles and Responsibilities 14
9. Abbreviations 15
10. Associated Documents and References 15
11. Training and Resources 16
12. Monitoring and Audit 16

Appendix 1 - NIHR Decision Tree for Adverse Event Reporting 17

1. Introduction

The purpose of this SOP is to lay out the requirements for safety reporting for University Sponsored Clinical Trials of Investigational Medicinal Products (CTIMPs), Clinical Investigations of Medical Devices (CIMDs), and other clinical research.

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (the Regulations) set out the requirements for adverse event management and reporting (pharmacovigilance) for all Investigational Medicinal Products (IMPs) used in CTIMPs. This requirement applies to all IMPs involved in the trial, whether it is the test drug or the comparator.

With regards to CIMDs Annex 7 of Directive 90/385/EEC[1] and Annex X of Directive 93/42/EEC[2] (as amended by Directive 2007/47/EC) states that *"all serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed."* See the European Commission Guidance Document – MEDDEV 2.7/3 for further details[3]. It is recognised that there are different definitions of adverse events for CIMDs and these are highlighted in the table below. It is also noted that for CIMDs adverse events can occur in both participants and users and both need to be reported and recorded.

To comply with the regulations, it is important that organisations undertaking the role of Sponsor have procedures and systems in place to support the recording, verification, reporting, analysis and management of adverse events and serious adverse events (suspected or unexpected).

Failure to report incidents or deal with incidents adequately can result in regulatory approval being withdrawn from an individual project or in extreme cases from all research carried out by the investigator.

An adverse event is an untoward medical occurrence in a patient which does not necessarily have a causal relationship with this treatment. This may include any unfavourable and unintended sign, an abnormal laboratory finding, symptom or disease temporally associated with the study drug.

Appendix 1 is the NIHR Decision Tree for Adverse Event Reporting, which can be used to accompany this SOP.

Definitions are provided in the sections below.

2. Scope of Procedure

This SOP will cover the processes for Pharmacovigilance and safety reporting for University Sponsored CTIMPs, CIMDs, and other clinical research.

[1] Active Implantable Medical Devices Directive (AIMDD)
[2] Medical Devices Directive (MDD)
[3] Guidance document - Clinical investigation, clinical evaluation - Clinical investigations: serious adverse event reporting - MEDDEV 2.7/3

3. Who

This SOP is aimed at staff within the University Clinical Directorate as well as Chief Investigators, students, trial coordinators and other members of University Staff involved in setup, management and conduct of University Sponsored CTIMPs, CIMDs, and other clinical research process for University Sponsored research.

4. When

This SOP should be referred to when a CTIMPs, CIMDs, and other clinical research is being set up to define Pharmacovigilance processes and safety reporting requirements as well as throughout the conduct of the trial.

The Sponsor is required to maintain accurate pharmacovigilance and safety records and ensure accurate and timely reporting of safety reports. For clinical research managed by a Clinical Trials Unit (CTU) this function is delegated to the Trial Coordinator and trial team, and for research not managed by a CTU this function is delegated to the CI and trial team. The following sections detail the requirements for the different types of Sponsored Research.

5. Clinical Trials of Investigations Medicinal Products (CTIMPs)

5.1 Definitions

Adverse events that require recording must be defined in the protocol. This should include events that may be none serious, but have been identified as being events of interest or important to the evaluation of the safety of the IMP. A risk-based approach should be taken when defining adverse events and so the protocol may also detail adverse events that may not be listed as expected events in the Reference Safety Information (RSI), but that are common events in disease progression and so do not require regulatory reporting.

Term	Definition
Adverse Event (AE)	An 'adverse event' is defined as per regulation 2(1) of the Clinical Trials Regulations as follows: Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with any intervention conducted due to the participant participation in the clinical trial, even if not associated to a medicinal product, should also be considered as an AE.

Term	Definition
Adverse Reaction (AR)	An 'adverse reaction' is defined in regulation 2(1) of the Clinical Trials Regulations as follows: any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship. An untoward and unintended response to a non-IMP should be recorded as an AR. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.
Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse event, serious adverse reaction or unexpected serious adverse reaction is defined in regulation 2(1) of the Clinical Trials Regulations as any adverse event, adverse reaction or unexpected adverse reaction, respectively, that– (a) results in death, (b) is life-threatening, (c) requires hospitalisation or prolongation of existing hospitalisation, (d) results in persistent or significant disability or incapacity, or (e) consists of a congenital anomaly or birth defect. These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which 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. Medical and scientific judgement should be exercised in deciding whether an event is 'serious' in accordance with these criteria. SAEs include all serious events independent of whether they have a suspected causal relationship to the investigational medicinal product (IMP) or not. Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences.

Term	Definition
	Such events (also referred to as 'important medical events') should also be considered as 'serious' in accordance with the definition. 'Serious' and 'severe' are not synonymous. Severity refers to the intensity of the event/reaction and is often classified by its effect on the everyday living of the participant as mild, moderate or severe. Seriousness refers to the outcome or action criteria of an AE or AR and serves as a guide for defining regulatory reporting. For example, a headache may be severe (prevents everyday activities) but is not considered serious (does not require inpatient hospitalisation, nor results in persistent disability/incapacity/congenital anomaly/birth defect and is neither life- threatening nor results in death).
Unexpected Adverse Reaction	An 'unexpected adverse reaction' is defined in regulation 2(1) of the Clinical Trial Regulations as follows: an adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in either (a) or (b) below. (a) in the case of a product with a marketing authorization, in the summary of product characteristics (SmPC), or equivalent document, for that product. (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question. Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events. For serious adverse reactions and determination of expectedness the version of the RSI at the moment of occurrence of the event applies, not the RSI at the time of case receipt by the sponsor. •
Other serious adverse events	Important medical events may not fall into the categories above, but may jeopardise the participant or require intervention to prevent one of the outcomes above. Those listed below should also be considered serious; • Overdoses (accidental or intentional) • Pregnancy (of participant or partner) • Any events and or laboratory abnormalities which are listed in the trial protocol as critical to safety evaluations and requiring reporting.

5.2 Adverse Event Reporting - CTIMPs

For all CTIMPs a pharmacovigilance plan must be finalised prior to 1st patient recruitment. This plan should detail the following;

- Responsibilities of the trial team and Independent Clinical Coordinators
- Reporting all adverse events including Non-Serious events to the Regulatory Authority, Ethics Committee and Sponsor
- Follow up of all adverse events
- The identification and role of the Independent Clinical Coordinators
- Identification of independent Trial Coordinators who can undertake unblinding if required
- Plan for testing the process
- Arrangements for Holiday/Sick cover
- Definition of the Reference Safety Information (RSI)
- Submission of the Development Safety Update Report (DSUR)
- Arrangements for reporting, recording and follow up in the event that a trial participant, or their partner becomes pregnant

The CTU or CI (hereafter parties delegate) must ensure an appropriate system is in place to record all adverse events relating to the clinical trial, as defined in the protocol in accordance with the afore mentioned Regulations. This must include events that do not require regulatory requirements. Investigators at sites will undertake an assessment of the event for seriousness and relatedness to the IMP(s) as per the protocol. They will then report the adverse event to the parties' delegate as defined in the protocol within **24 hours** of becoming aware of the event.

Where an adverse reaction is deemed to be a SUSAR the parties delegate must ensure reporting in line with the below timeframes;

SUSARs (fatal or life threatening)

Must be reported to the following bodies no later than **7 calendar days** after the parties' delegate become aware of the reaction;

- The MHRA – reported through ICSR Submissions (for submitting single SUSARs) or the MHRA Gateway (for submitting single or bulk reports) using the E2B (R3) format.
- The competent authorities of any European Economic Area (EEA) state other than the UK where the trial is being conducted

A follow up report with any relevant information should be submitted within a further **8 calendar days.**

SUSARs (all other)

Must be reported to the same bodies as above no later than **15 calendar days** after the parties' delegate become aware of the reaction.

5.3 Annual Safety Reporting for CTIMPs (DSUR)

Under regulation 35 of the Clinical Trials Regulations, for each IMP tested in a clinical trial in the UK, the sponsor must provide the MHRA with an annual report on the safety of the participants receiving the product. This annual report should be in the form of a Development Safety Update Report (DSUR). It is usually expected that one DSUR is submitted per IMP, however in some cases the MHRA will accept a DSUR for an individual trial. Justification for this approach must be provided. It is expected that University Sponsored CTIMPs using the same IMP will submit separate DSURs, but they must reference other trial(s) (including EduraCT number, title and date of last DSUR submission).

In addition to the DSUR, the licensing authority may ask for a list of SARs and SAEs that have occurred at any time during the reporting year to be provided within 30 days of the request (or another timeline specified by the licensing authority). This may follow review of a DSUR, for example, or at any other time if a safety concern regarding a trial or its participants has come to its attention.

The Sponsor must provide the MHRA with a Development Safety Update Report (DSUR) within 60 calendar days of the data lock point following the Development International Birth Date (DIBD) of the clinical trial each year. This is usually the date of first authorisation of the clinical trial in any country. The aim of the DSUR is to provide full ongoing safety information for the IMP for all competent authorities around the world.

The DSUR should follow the headings in section 3 of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidance on Development Safety Update Report (E2F), clearly indicating if a section is not applicable. ICH E2F can also be referenced for additional detail on the content outlined below.

Per regulations A32 and 35 of the Clinical Trials Regulations, the DSUR must include the following:

- records of any serious adverse reactions (SARs) and serious adverse events (SAEs) which have occurred in clinical trials during that year, including suspected SUSARs, preferably provided as an aggregate summary tabulation
- evaluation of these SARs and SAEs, which should be from a global perspective, including any limitations to the evaluation, and evaluation of any changes in the overall risk-benefit
- records of any measures taken to investigate, minimise and prevent the risks presented by SARs and SAEs

- a detailed description of the assessment and management of any serious or non-serious safety concerns, including (but not limited to) temporary halts, actions taken by another regulatory authority, urgent safety measures, serious breaches, Dear Investigator letters, and specific non-clinical or clinical events

To submit a DSUR to the licensing authority:

- if at least one of the clinical trials covered by the DSUR was approved through the combined review process, submit the report through IRAS. Guidance on using IRAS to submit a DSUR can be found in the Step-by-step guide to using IRAS for combined review
- if all the clinical trials covered by the DSUR were approved through separate applications to the licensing authority and the ethics committee, submit the report through MHRA Submissions

6. Clinical Investigations of Medical Devices (CIMDs)

6.1 Definitions

Term	Definition
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including abnormal lab findings) in participants, users or other persons whether or not related to the investigational medical device • Note 1 – this includes events related to the investigational devices, or the comparator • Note 2 – this definition includes events related to the procedures involved • Note 3 – for users or other persons this definition is restricted to events related to investigational medical devices. *For example* • A patient, user or carer or professional is injured as a result of a medical device failure or its misuse; • A patient's treatment is interrupted or compromised by a medical device; • A misdiagnosis, due to a medical device failure, leads to inappropriate treatment; • A patient's health deteriorates due to medical device failure. Causes my included: design, poor user instructions or training; inappropriate modifications; inadequate maintenance and unsuitable storage and use conditions

Serious Adverse Event (SAE)	An adverse event that
	• Led to a death, injury or permanent impairment to a body structure or a body function;
	• Led to a serious deterioration of health of the participant that resulted in;
	  ○ A life-threatening illness or injury;
	  ○ A permanent impairment of a body structure of a body function;
	  ○ In-patient hospitalisation or prolongation of existing hospitalisation;

Term	Definition
	○ Medical or surgical intervention to prevent life threatening illness. • Led to foetal distress, foetal death or congenital abnormality or birth defect. NOTE – Planned hospitalisation for pre-existing condition, or a procedure required by the protocol or clinical investigation plan (CIP) without serious deterioration in health is not usually considered to be an SAE
Device deficiency	Inadequacy of an Investigation Medical Device related to its identity, quality, durability, reliability, safety or performance This may include malfunctions, user error or inadequacy in the information supplied by the manufacturer.
Adverse Device Effect (ADE)	Adverse event 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. This includes any event that is a result of a user error or intentional abnormal use of the investigational medical device.
Serious Adverse Device Effect (SADE)	An adverse device effect that results in any of the consequences characteristic of a SAE.
Unanticipated Serious Adverse Device Effect (USADE)	A SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report Note: Anticipated SADE (ASADE) an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.
Other serious adverse events	Important medical events may not fall into the categories above, but may jeopardise the participant or require intervention to prevent one of the outcomes above. Those listed below should also be considered serious; • Overdoses (accidental or intentional) • Pregnancy (of participant or partner)

Term	Definition
	• Any events and or laboratory abnormalities which are listed in the trial protocol as critical to safety evaluations and requiring reporting.

5.2 Adverse Event Reporting - CIMDs

The Sponsor of CIMDs is required to record and report safety events. For CIMDs managed by a Clinical Trials Unit (CTU) this function is delegated to the Trial Coordinator and trial team, and for CIMDs not managed by a CTU this function is delegated to the CI and trial team.

For all CIMDs a device vigilance plan must be finalised prior to 1st patient recruitment.

CIs and research teams working on CIMDs are recommended to refer to the European Commission Guidance document for adverse event reporting (MEDDEV 2.7/3).

This plan should detail the following;

- Responsibilities of the trial team and Independent Clinical Coordinators
- Reporting all adverse events including Non-Serious events to the Regulatory Authority, Ethics Committee and Sponsor
- Follow up of all adverse events
- The identification and role of the Independent Clinical Coordinators
- Identification of independent Trial Coordinators who can undertake unblinding if required
- Plan for testing the process
- Arrangements for Holiday/Sick cover

The CTU or CI (hereafter parties delegate) must ensure an appropriate system is in place to record all adverse events relating to the clinical trial in accordance with the afore mentioned Regulations.

There should be an implemented system to ensure that reportable events are communication from any Principle Investigators to the parties' delegate **immediately, but no later than 3 calendar days** following the awareness of the event at site.

All SAEs and any Device Deficiency that might have led to an SAE, whether initially considered to be device-related or not, must be reported to the **MHRA** in line with the below timelines;

- Where a reportable event indicates an imminent risk of death, serious injury or serious illness it must be reported **immediately**, but not later than **2 calendar days** after awareness of the event.

- All other reportable events must be reported **immediately**, but not later than **7 calendar days** after awareness of the event.

All SAEs and any Device Deficiency that might have led to an SAE, whether initially considered to be device-related or not, must be reported to the **REC** in line with the below timelines;

- Where a reportable event indicates an imminent risk of death, serious injury or serious illness it must be reported **immediately**, but not later than **2 calendar days** after awareness of the event.

- All SAEs which are related to the device and unexpected must be reported **immediately**, but not later than **15 calendar days** after awareness of the event.

The EC provide an SAE reporting template[4] which should be used to report all reportable events. The table gives a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to participating National Competent Authorities (NCAs) each time a new reportable event or a new finding to an already reported event is to be reported. More detailed information has to be provided on request of an NCA, if so requested by using the individual reporting form. The delegated party shall identify the new/updated information in the status column of the tabular form as:

- a = added = new reportable event;
- m = modified = new finding/update to an already reported event;
- u = unchanged.

7. Other clinical research

In non-regulated clinical research other than CTIMPs or CIMDs, a serious adverse event (SAE) is defined as an untoward occurrence that:

a) results in death;

b) is life-threatening;

c) requires hospitalisation or prolongation of existing hospitalisation;

d) results in persistent or significant disability or incapacity;

e) consists of a congenital anomaly or birth defect;

f) or is otherwise considered medically significant by the investigator.

An SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator (CI) the event was:

[4] http://ec.europa.eu/DocsRoom/documents/16477

- Related – that is, it resulted from administration of any of the research procedures,

and

- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence

Research approved by an NHS REC should report above such events to the REC that approved the research within 15 days of the CI becoming aware of the event. The HRA provide specific guidance and a submission form that should be used to report SAEs[5].

8. Roles and Responsibilities

Where the sponsor is listed below it is noted that the function is carried out by parties' delegate with oversight from the Sponsor.

The Sponsor ensures SUSAR's occurring in CTIMPs are reported to MHRA within 7 days if fatal and 15 days if non-fatal;

The Sponsor ensures reportable SAEs and Device Deficiencies occurring in CIMDs are reported to MHRA and REC within the afore mentioned timelines;

The Sponsor should ensure follow-up reports are provided in a timely manner;

The Sponsor should ensure all Investigators are provided with information on any urgent safety measures within 7 working days;

The Sponsor has responsibility for ensuring Development Safety update reports are submitted within 60 calendar days of the DIBD;

The Sponsor must undertake urgent safety measures if required;

The PI is responsible for ensuring all SAEs and SUSARs are reported to the Sponsor in a timely manner;

The Sponsor is ultimately responsible for deciding if a sponsored study should halt recruitment based on an adverse event. This responsibility is undertaken by the chair of the Liverpool Health Partners (LHP) Joint Research Office (JRO) Sponsorship Committee, or their appointed deputy. The Senior Clinical Research Governance Manager will ensure review is undertaken of adverse events that may affect recruitment continuation.

[5] http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/

9. Abbreviations

ADE Adverse Device Effect

AE Adverse event

AR Adverse reaction

CI Chief Investigator

CIMD Clinical Investigation of Medical Device

CTIMP Clinical Trial of an Investigational Medicinal Product

CTU Clinical Trials Unit

GCP Good Clinical Practice

IMP Investigational medicinal product

JRO Joint Research Office

LHP Liverpool Health Partners

MHRA Medicines and Healthcare Products Regulatory Agency

NCA National Competent Authority

PI Principal Investigator

REC Research Ethics Committee

SADE Serious Adverse Device Effect

SAE Serious Adverse Event

SOP Standard Operating Procedure

SUSAR Suspected Unexpected Serious Adverse reactions

USADE Unanticipated Serious Adverse Device Effect

10. Associated Documents and References

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025

The Medical Devices Regulations 2002

ICH Harmonised Guideline for Good Clinical Practice E6(R3)

https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

MHRA eSUSAR reporting guidance

REC Guidance

Guidance document - Clinical investigation, clinical evaluation - Clinical investigations: serious adverse event reporting - MEDDEV 2.7/3

Active Implantable Medical Devices Directive (AIMDD)

Medical Devices Directive (MDD)

Directive 2007/47/EC

11. Training and Resources

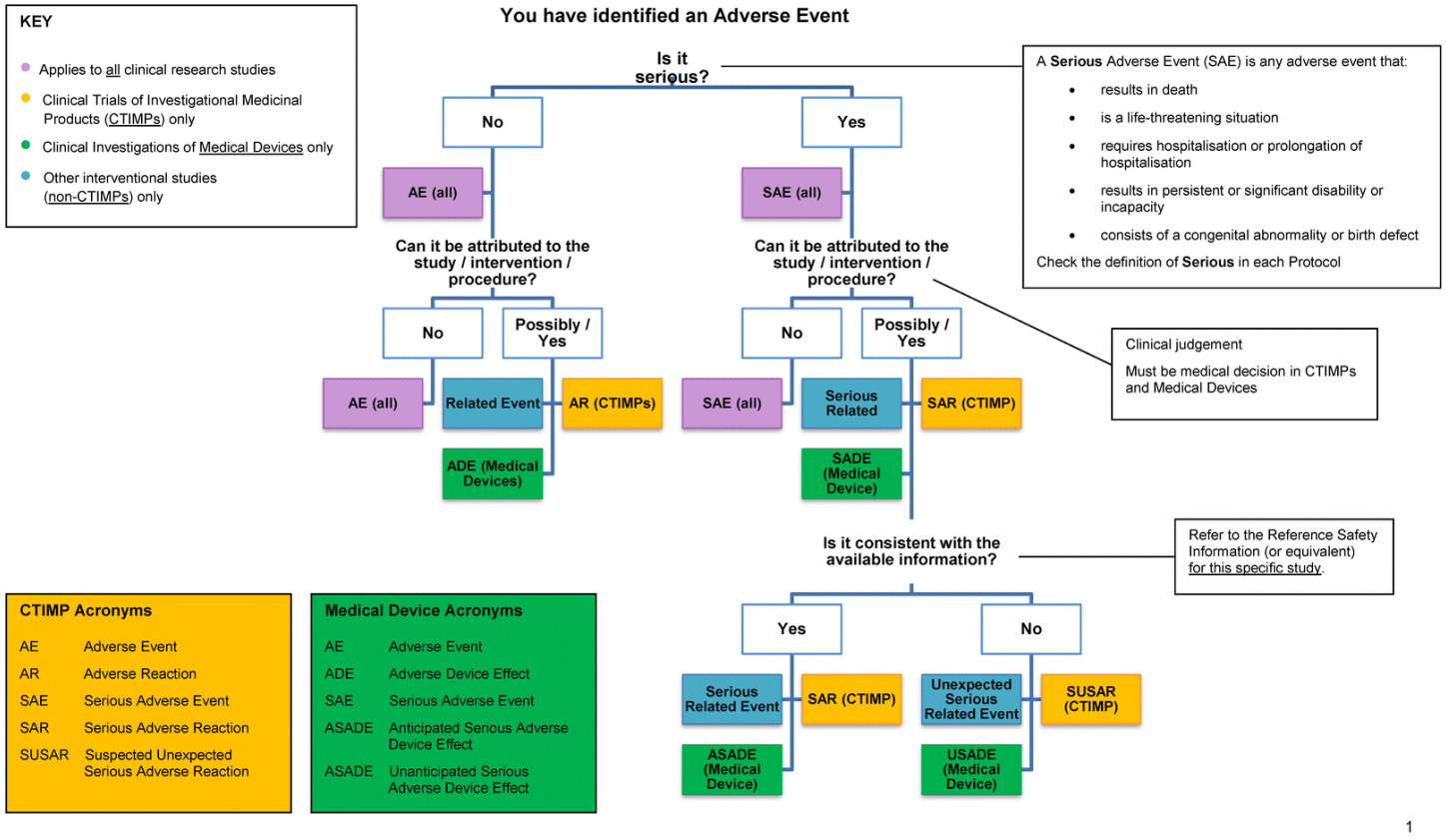
CIs, students, trial coordinators and other members of University Staff involved in safety reporting activities should be aware of and familiar with this SOP. Training can be provided by the Clinical Research Governance Team upon request.

Members of University staff with responsibility for assessing severity of adverse events must be appropriately qualified and trained to undertake the role.

12. Monitoring and Audit

An internal audit of Clinical Directorate SOPs will be conducted at a minimum of every two years.

Appendix 1 - NIHR Decision Tree for Adverse Event Reporting

NIHR | National Institute for Health and Care Research

Decision Tree for Adverse Event Reporting – ALL STUDIES