Research Governance Standard Operating Procedure 9 – Safety reporting

Document details		
Version	V1.2 24/04/2026	
Effective from	28/04/2026	
Review date	28/04/2028	
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Superseded documents	v1.1	

Document history						
Version	Review date	Reviewer	Section(s) Amended	Updated version	Approver	Effective date
v1.0	10/03/2025	Adam Taylor	Review date corrected	V1.1	Adam Taylor	10/04/2025
V1.1	23/04/2026	Emily Avent	Regulation updates	V1.2	Rachel Davies	28/04/2026

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1. Glossary

Terminology is explained in the Research Governance Glossary, the most recent version of which can be found **on the Research Governance webpages.**

2. Background

This SOP explains how members of the RGT, in particular the **RHTM**s and **RGO**s, should review those parts of study documentation concerned with safety reporting when preparing that study for sponsorship. In particular, it explains what wording and information should be used depending on whether the study is a CTIMP, CIMD, or neither, and which reporting requirements should be in place. It describes these in light of the regulatory and legal requirements in place within the setting of the **Medicines for Human Use (Clinical Trials) Regulations 2004,** as amended by the **Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025,** the **Medical Devices Regulations 2002,** and the **UK Policy Framework for Health and Social Care Research**.

For CTIMPS, it is RGT's responsibility as Sponsor to "keep detailed records of all serious adverse events and serious adverse reactions, including suspected unexpected serious adverse reactions, which occur during the course of a clinical trial" **UK Clinical Trials Regulations**.

The following terminology will be used throughout:

Adverse event (AE): Any untoward medical occurrence in a study participant. The occurrence need not be related to study participation. The occurrence can be new in onset, aggravated in severity or frequency from the baseline condition, or an abnormal result of diagnostic procedures, including laboratory test abnormalities.

> Adverse events are the ultimate constituent of all safety events. The other events described below are all adverse events which meet additional criteria (causality, seriousness, unexpectedness). Therefore when a protocol says, for instance, that all adverse events must be recorded, this includes adverse reactions, serious adverse events, serious adverse reactions and SUSARs; when a protocol says, for instance, that all SAEs must be reported to the Sponsor, this includes serious adverse reactions and SUSARs.

Adverse reaction (AR): An adverse event that is determined by a clinician to be possibly, probably or definitely related to study participation.

***CIMD only* – Adverse device effect (ADE):** An adverse event that is related to the use of an Investigative Medical Device.

Serious adverse event (SAE): An adverse event that:

- Results in the death of the participant
- Is life-threatening
    - The term "life-threatening" 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 might have caused death if it had progressed in severity.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation

    - Typically considered to be an overnight stay or other admission to an inpatient facility.
    - Exceptions to this are hospitalisations for:
        - social reasons in absence of an adverse event
        - in-patient protocol procedures
        - surgery or procedure planned before entry into the study
- Results in persistent or significant disability / incapacity
    - Any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.
- Is a congenital anomaly / birth defect
- Is an Important Medical Event; an adverse event that does not meet any of the above SAE criteria but, in the clinical opinion of an investigator, requires expedited reporting.

***CIMD only* – Serious adverse device effect (SADE):** An adverse device event that:

- Results in the death of the participant,
- Is life-threatening,
    - The term "life-threatening" 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.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
    - Typically considered to be an overnight stay or other admission to an inpatient facility.
    - Exceptions to this are hospitalizations for:
        - social reasons in absence of an adverse event
        - in-patient protocol procedures
        - surgery or procedure planned before entry into the study (must be documented in the CRF)
- Results in persistent or significant disability / incapacity,
    - Any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.
- Is a congenital anomaly / birth defect

Serious adverse reaction (SAR): A serious adverse event that is determined by a clinician to be possibly, probably or definitely related to the study product, procedure or intervention, i.e.:

- Alternative explanations for the reaction, such as concomitant drugs, or diseases, are inconclusive; the relationship in time is reasonable and a causal relationship cannot be excluded, and/or
- The relationship in time is suggestive (e.g. confirmed by withdrawal of the study product, procedure or intervention), and alternative explanations, such as concomitant drugs, or diseases, are less likely, and/or
- The relationship cannot be reasonably explained by an alternative explanation, such as concomitant drugs or diseases. The relationship in time is very suggestive (e.g. confirmed by withdrawal and re-introduction of the study product, procedure or intervention).

Suspected unexpected serious adverse reaction (SUSAR): An serious adverse reaction that is *unexpected*, i.e. the nature or severity of the event is not listed in the Reference Safety

Information/Summary of Product Characteristics/Investigator Brochure, as specified in the Clinical Trial Agreement.

***CIMD only* – Unanticipated serious adverse device effect (USADE)**: An adverse event that is serious, related to the IMD, and the occurrence of which is, or characteristics of which are, not consistent with the information in the Clinical Investigator Plan, Investigator Brochure or risk analysis report.

> Suspected unexpected serious adverse reactions and unanticipated serious adverse device effects are the most significant events in a trial as they provide new information about the safety of participants in the trial that may require immediate action.

Severity: A clinical assessment of the effect or intensity of an event upon a patient. Typically classed as *mild* – having no or almost no impact on the participant's routine activities or quality of life, *moderate* – having a noticeable impact on the participant's routine activities or quality of life, or *severe* – resulting in the participant being partly or wholly incapacitated. This is a distinct clinical assessment, unrelated to the seriousness of an event (see above).

***CIMD only* – Device deficiency:** The **"**inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance [including] malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling." (ISO141155)

3. Scope

This SOP only covers the review of study documentation by members of the RGT, where that study is sponsored by the University. This SOP does not cover the actual management, or actual reporting, of adverse events. This is managed by UHBW on behalf of the University under a Service Level Agreement.

4. Responsibilities

This SOP is applicable to the **RHTMs** and **RGOs** when they are reviewing studies prior to sponsorship. It should be used in conjunction with the **RG SOP 6 – Sponsoring a study**.

5. Procedure

5.1. CTIMPs

There are strict legal requirements for recording, reporting and acting around patient safety events within CTIMPs, grounded in the **UK Clinical Trials Regulations** legislation and enforced by the MHRA. The RGT member reviewing the protocol should ensure the following:

- That definitions of *adverse event, adverse reaction, serious adverse event and suspected unexpected serious adverse reaction* are accurate. The precise wording in the definitions given above is not required, but the meaning conveyed should be the same as in this SOP.
- Any reporting processes are clearly articulated, stated in one part of the protocol only, and internally consistent.
- Any reporting processes are sufficiently clear that the research team can operationalise them once the study is live.
- The recording period for participants is stated correctly; typically this is either from the point at which the participant signs the consent form, or from the first dose of the IMP until a fixed period after their final dose of the IMP, or study end (unless a participant withdraws their consent to participate or for follow-up).

- Where studies have been agreed by all parties to be lower risk (typically phase 4 studies of licensed medication) the sponsor may agree to less strict reporting requirements. The sponsor will assess this on the basis of the university's willingness to accept risk to participants, and will advise on what is likely to be acceptable to an ethics committee and the MHRA. Once agreed during study review, these deviations will need to be approved by the REC and the MHRA before implementation.
- If the agreed processes deviate from those described in the **International Council for Harmonisation's Guideline for Good Clinical Practice** (typically referred to as ICH E6), all references to compliance with this standard should be removed.

The responsible RGT member should ensure that the following recording, reporting and actions are specified in the protocol, unless a deviation has been agreed as above. They do not need to impose the precise wording or format used below but they should ensure that the protocol wording is at least consistent with this, and moreover that the descriptions of recording, reporting and actions in the protocol are clear, sufficiently detailed and non-contradictory.

	AE	AR	SAE	SUSAR
Recording	The AE and any measures taken must be recorded within both the CRF and source document by an appropriately delegated individual. The record should include a clear description of the nature of the event, a MedDRA classification where appropriate, and sufficient information to determine which other categories (seriousness, relatedness, expectedness) apply to the event.	The AR and any measures taken must be recorded within both the CRF and the source document by an appropriately delegated individual. The record should include a clear description of the nature of the event, a MedDRA classification (where appropriate) and sufficient information to determine which other categories (seriousness, relatedness, expectedness) apply to the event.	The SAE and any measures taken must be recorded within both the CRF and the source document by an appropriately delegated individual, with the information that it meets serious criteria. The record should include a clear description of the nature of the event, a MedDRA classification (where appropriate) and sufficient information to determine which other categories (seriousness, relatedness, expectedness) apply to the event. The SAE should also be recorded in an SAE form as part of the reporting process (described below).	The SUSAR and any measures taken must be recorded within both the CRF and the source document by an appropriately delegated individual, with the information that it meets serious and unexpected criteria. The record should include a clear description of the nature of the event, a MedDRA classification (where appropriate) and sufficient information to determine which other categories (seriousness, relatedness, expectedness) apply to the event. The SUSAR should also be recorded in a SUSAR form as part of the reporting process (described below).
Reporting	There is no requirement of Expedited Reporting for adverse events.	There is no requirement of Expedited Reporting for adverse reactions.	All SAEs must be reported to the sponsor not more than 24 hours after the trial team become aware of them. Any further required information should be provided to the sponsor within 72 hours of the trial team becoming aware of the SAE. The SAE should be reported in the format agreed for this study (often, but not always, the UHBW SAE reporting form). The format must include an assessment of SAE expectedness, relatedness, and event status (for instance, whether the event is ongoing, resolved, resolved with sequelae, deceased). Much of an SAE form can be completed by any appropriately delegated member of staff. However, an Investigator must review relatedness and severity *at minimum*. Likewise, only an Investigator may sign off the form. Other parties should be informed as required by the protocol. Where an SAE is unresolved at submission of the report, it should be followed until resolution, beyond study end if necessary.	An initial report of a SUSAR will be made, as per an SAE, within not more than 24 hours of the trial team being made aware. When a sponsor receives a SUSAR report, they should immediately contact the CI to ensure they have also been informed. The CI should notify any other parties as described in the protocol. If the SUSAR is ongoing, further information should be provided to the sponsor as soon as it is available. The CI or the sponsor may determine that an evert reported as an SAE or SAR is a SUSAR and needs to be managed as such. However events reported as a SUSAR must be investigated on that basis, and neither the sponsor, the CI, or any other Investigator can reclassify the SUSAR as a lesser event. All relevant information about a SUSAR must be reported to the MHRA (for CTIMPs submitted through Combined Review). SUSARs that are fatal or life-threatening must be reported as above within 7 days from Sponsor being made aware. All other SUSARs must be reported, as above, within 15 days. Where a SUSAR is unresolved at submission of the report, it should be followed until resolution, including beyond study end if necessary.
Action	There are no specific actions associated with adverse events.	There are no specific actions associated with adverse reactions.	The sponsor and CI should determine whether any other categories apply to the SAE and if any additional reporting needs to happen.	The sponsor, CI, ethics committee and MHRA will determine whether action needs to be taken to protect patient safety. This may involve an urgent safety measure

SAEs not requiring expedited reporting
It may be determined during study design that, in light of the patient population or the trial treatment, certain events or types of events are likely to be common, and that consequently the reporting all such events as SAEs will be impractical and unhelpful. These events may be listed in the safety reporting section of the protocol, explaining that standard expedited reporting will not be followed. The RGT member reviewing the protocol should ensure that it is clearly stated how such events will be recorded, reported and managed.

It is important that these events not be confused or conflated with events which are expected reactions to an IMP or anticipated reactions to a Medical Device. In the interests of clarity, if these events are named in a protocol, the protocol should use either the opposite term (i.e. anticipated for a CTIMP, expected for a CIMD), or a different term entirely.

5.2 CIMDs
There are strict legal requirements for recording, reporting and acting around patient safety events within CIMDs, grounded in the **Medical Devices Regulations 2002** legislation and regulated by the MHRA. These requirements must be followed. The RGT member reviewing the protocol should ensure that:

- Definitions of *adverse event*, *adverse device event, adverse reaction*, *serious adverse event*, *serious adverse device event, suspected unexpected serious adverse reaction* and *unanticipated serious adverse device effect* are accurate. The precise definitions given above do not need to be used, but their content should be the same.
- Any reporting processes are clearly articulated, stated in one part of the protocol only, and internally consistent.
- The recording period for participants is stated correctly; typically this is either from the point at which the participant signs the consent form, or from the initiation of the IMD intervention until a fixed period after the end of the IMD intervention, or study end (unless a participant withdraws their consent to participate or for follow-up).
- The recording period for participants is stated correctly; typically this is from the point at which the participant signs the consent form until their withdrawal or study end, whichever is sooner.
- If the agreed processes deviate from those described in the **International Council for Harmonisation's Guideline for Good Clinical Practice** (typically referred to as ICH E6), all references to compliance with this standard should be removed. Deviation from MHRA reporting rules requires agreement from both the sponsor and MHRA; historically, the MHRA have been unwilling to grant this.

The RGT member reviewing the protocol should assess the reactions listed in the RSI, Manufacturers Product Information, and CIP/IB, and confirm that those *anticipated events* expedited from immediate reporting by the study team are in the documentation, and that their exclusion is proportionate; that they are not excluding items which require expedited reporting, and that they have not neglected to exclude items which do not require expedited reporting.

The responsible RGT member should ensure that the following recording, reporting and actions are specified in the protocol, unless a deviation has been agreed as above. They do not need to impose the precise wording or format used below but they should ensure that the protocol wording is at least consistent with this, and moreover that the descriptions of recording, reporting and actions in the protocol are clear, sufficiently detailed and non-contradictory.

	AE	ADE	SAE/SADE	USADE
Recording	The AE and any measures taken must be recorded within both the CRF and source document by an appropriately delegated individual. The record should include a clear description of the nature of the event, a MedDRA classification where appropriate, and sufficient information to determine which other categories (seriousness, relatedness, expectedness) apply to the event.	The ADE and any measures taken must be recorded within both the CRF and the source document by an appropriately delegated individual. The record should include a clear description of the nature of the event, a MedDRA classification (where appropriate) and sufficient information to determine which other categories (seriousness, relatedness, expectedness) apply to the event.	The SAE/SADE and any measures taken must be recorded within both the CRF and the source document by an appropriately delegated individual, with the information that it meets serious criteria. The record should include a clear description of the nature of the event, a MedDRA classification (where appropriate) and sufficient information to determine which other categories (seriousness, relatedness, expectedness) apply to the event. The SAE/SADE should also be recorded in an SAE/SADE form as part of the reporting process (described below).	The USADE and any measures taken must be recorded within both the CRF and the source document by an appropriately delegated individual, with the information that it meets serious and unexpected criteria. The record should include a clear description of the nature of the event, a MedDRA classification (where appropriate) and sufficient information to determine which other categories (seriousness, relatedness, expectedness) apply to the event. The USADE should also be recorded in a USADE form as part of the reporting process (described below).
Reporting	There is no requirement of Expedited Reporting for AEs.	There is no requirement of Expedited Reporting for ADEs.	All SAEs/SADEs must be reported to the sponsor not more than 24 hours after the trial team become aware of them. Any further required information should be provided to the sponsor within 72 hours of the trial team becoming aware of the SAE/SADE. The SAE/SADE should be reported in the format agreed for this study (often, but not always, the UHBW SAE reporting form). The format must include an assessment of SAE/SADE expectedness or anticipatedness, relatedness, and event status (for instance, whether the event is ongoing, resolved, resolved with sequelae, deceased). Much of an SAE/SADE form can be completed by any appropriately delegated member of staff. However, an Investigator must review relatedness and severity *at minimum*. Likewise, only an Investigator may sign off the form. Where the SAE or related IMD deficiency risks death, serious injury or illness, it must be reported by the CI and sponsor to the MHRA within 48 hours of the sponsor being made aware, using the MHRA form. SAEs or IMD deficiencies which do not meet these criteria should be reported by the CI and sponsor to the MHRA within seven calendar days of the sponsor becoming aware, again using the MHRA form. In both cases, these SAE/SADEs should be reported by the CI and sponsor even if there is no relatedness between the event and the study device/intervention. Other parties should be informed as required by the protocol. Where an SAE/SADE is unresolved at submission of the report, it should be followed until resolution, beyond study end if necessary.	An initial report of a USADE will be made, as per an SAE, within not more than 24 hours of the trial team being made aware. When a sponsor receives a USADE report, they should immediately contact the CI to ensure they have also been informed. The CI should notify any other parties as described in the protocol. If the USADE is ongoing, further information should be provided to the sponsor as soon as it is available. The CI or the sponsor may determine that an evert reported as an SAE or SAR is a USADE and needs to be managed as such. However events reported as a USADE must be investigated on that basis, and neither the sponsor, the CI, or any other Investigator can reclassify the USADE as a lesser event. All relevant information about a USADE must be reported to the MHRA and the NHS REC by the sponsor and CI. If the study was submitted through combined review this is a single process. USADEs that are fatal or life-threatening must be reported as above within 7 days. All other USADEs must be reported, as above, within 15 days. Where a USADE is unresolved at submission of the report, it should be followed until resolution, including beyond study end if necessary.
Action	There are no specific actions associated with AEs.	There are no specific actions associated with ADEs.	The sponsor and CI should determine whether any other categories apply to the SAE/SADE and if any additional reporting needs to happen.	The sponsor, CI, ethics committee and MHRA will determine whether action needs to be taken to protect patient safety. This may involve an urgent safety measure

SAEs/SADEs not requiring expedited reporting
It may be determined during study design that, in light of the patient population or the trial treatment, certain events or types of events are likely to be common, and that consequently the reporting all such events as SAE/SADEs will be impractical and unhelpful. These events may be listed in the safety reporting section of the protocol, explaining that standard expedited reporting will not be followed. The RGT member reviewing the protocol should ensure that it is clearly stated how such events will be recorded, reported and managed.

It is important that these events not be confused or conflated with events which are expected reactions to an IMP or anticipated reactions to a Medical Device. In the interests of clarity, if these events are named in a protocol, the protocol should use either the opposite term (i.e. anticipated for a CTIMP, expected for a CIMD), or a different term entirely.

5.3 Non-CTIMP/CIMDs

There are no legislative reporting requirements for non-CTIMP/CIMD studies. The **UK Policy Framework** and associated **Good Clinical Practice** requirements mandate that participant safety is protected at all times. Besides this, the RGT member reviewing the protocol should check that:

- Where used, definitions of AE, AR, SAE and SUSAR are accurate.
- Any reporting processes are clearly articulated, stated in one part of the protocol only, and internally consistent.
- Any reporting processes are sufficiently clear that the research team can operationalise them once the study is live.
- Any reporting processes are sufficiently clear that an ethics committee can readily assess *what* the reporting plan of the research team is, and *whether* it is commensurate with the level of study risk.
- The recording period for participants is stated correctly; typically this is from the point at which the participant signs the consent form until their withdrawal or study end, whichever is sooner.
- That those *anticipated events* described in the documentation, which the study team propose to exclude from immediate reporting, are proportionate; that no items requiring such exclusion have been left out.
- That the reporting process described is appropriate to the risk of the study:
    - High risk intervention: These non-CTIMPs/CIMDs will require correspondingly robust reporting, up to and including the reporting standards applied to CTIMP/CIMD studies. The process described in the protocol should be more detailed to support this, with thorough definition of AEs, ARs, SAEs and SUSARs, and information about anticipated events that would not be immediately reported.
    - Moderate risk intervention: Less directly interventional studies, involving changes to care pathways, GP guidance, or other shifts in care may not require CTIMP-level reporting. For instance, the protocol may promise only to report SUSARs to the REC, or both SUSARs and SAEs but with the latter more slowly and in aggregate. The protocol may characterise in less detail what SUSARs and SAEs are (for instance, excluding the considerations around non-clinically mandated hospital stays typically cited in CTIMP descriptions of seriousness).

- Low risk intervention: Interventions such as blood draws or questionnaires where the likelihood of related incidents is sufficiently minimal *may* be consistent with very limited reporting to the REC – for instance, a single paragraph defining a SUSAR and explaining that only these would be reported. Moreover, the description of the safety reporting process in the protocol can be correspondingly brief. For studies where there is no risk of related incidents (perhaps data-only research, or some qualitative work), it can be permissible to have no reporting to the REC whatsoever. However, this decision and its rationale needs to be clearly documented within the protocol and IRAS application.

6. Related documents

Internal documents

RG SOP 6 – Sponsoring a study

External documents

UK Policy Framework for Health and Social Care Research

ICH E6 (R3) GCP

The Medical Devices Regulations 2002

UK Clinical Trials Regulations