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| **Reference Number:** UHB 253<br>**Version Number:** 5.0 | **Date of Next Review:** 24/02/2029 |

# Cardiff Joint Research Office (JRO) Standard Operating Procedure (SOP) for Safety Reporting in Clinical Trials of Investigational Medicinal Products (CTIMPs)

## Introduction and Aim

In clinical research, the safety and well-being of all research participants must always prevail over the interests of science and society. The reporting of safety events is one of the most important aspects of clinical trial management.

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (as amended) (hereinafter referred to as the UK Clinical Trials Regulations) requires all safety events arising in Clinical Trials of Investigational Medicinal Products (CTIMPs) to be appropriately recorded and reported. To breach these requirements constitutes a breach in law. In accordance with the UK Policy Framework for Health and Social Care Research and the Clinical Trials Regulations, all Sponsors must have systems in place to record and report adverse events, serious adverse events and serious adverse reactions (including Suspected Unexpected Serious Adverse Reactions (SUSARS), and to provide regular safety updates to the relevant authorities.

This joint procedure aims to detail the expectations for safety recording and reporting in CTIMPs which are Sponsored by Cardiff University (CU) or Cardiff and Vale UHB (CAVUHB) or Hosted by CAVUHB.

## Objectives

- To ensure that safety recording and reporting in CTIMPs which are Sponsored by CU or CAVUHB or Hosted at CAVUHB is conducted in compliance with the UK Clinical Trial Regulations;
- To ensure that the responsibilities for safety reporting in CU and CAVUHB Sponsored CTIMPs are clearly outlined;
- To ensure that Chief Investigators (CIs) and their delegates are aware of the safety reporting and recording requirements for CTIMPs Sponsored by CU or CAVUHB or Hosted by CAVUHB;
- To ensure that the process for identifying and reporting Urgent Safety Measures (USM) in CTIMPs which are Sponsored by CU or CAVUHB or Hosted at CAVUHB is clear;
- To ensure that the annual safety reporting requirements for CTIMPs which are Sponsored by CU or CAVUHB or Hosted at CAVUHB are clear.

## Scope

This procedure applies to all individuals who are leading, or who are delegated to work, on any aspect of a CU or CAVUHB Sponsored CTIMP.

It also applies to the expectations for safety reporting in commercial or non-commercial Sponsored CTIMPs which are hosted at CAVUHB, where CAVUHB holds any delegated responsibility for safety recording and reporting. This includes individuals:

- holding substantive or honorary contracts/titles with CAVUHB;
- holding official 'letters of access' issued by CAVUHB;
- who are undertaking CTIMPs involving CAVUHB patients or staff;
- Who are undertaking CTIMP activity on CAVUHB premises.

This procedure does not apply to the safety reporting processes for clinical research which does not fall under the scope of the UK Clinical Trial Regulations (i.e. non-CTIMPs). For guidance on safety reporting in research studies other than CTIMPS (non-CTIMPs) please refer to the CAVUHB Information Sheet Adverse Event and Serious Adverse Event reporting requirements for non CTIMPs (IS/001/06).

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| **Equality Health Impact Assessment** | An Equality Impact Assessment has been completed on the Research Governance Policy (UHB 099) under which this SOP sits.<br>The Equality Impact Assessment completed for the policy found there to be a no impact. |
| **Documents to read alongside this Procedure** | • The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025<br>• UK Policy Framework for Health and Social Care Research 2017 (as amended)<br>• Research Governance Policy (UHB 099)<br>• ICH GCP E6 (R3)<br>• The Safety Reporting SOPs and associated documents in place with the relevant Clinical Trials Unit (CTU) responsible for managing Pharmacovigilance and Safety Reporting for the CTIMP<br>• The Cardiff Joint Research Office (JRO) SOP for Applying for Sponsorship of Higher Risk Studies (including Clinical Trials of Investigational Medicinal Products (CTIMPs) and Clinical Trials of Medical Devices (Medical Device Trials)) (SOP-001-05) |
| **Approved by** | Clinical Trials Governance Group<br>Joint Research Governance Group |

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| **Accountable Executive or Clinical Board Director** | Medical Director |
| **Author(s)** | JRO Research Governance Team |

**Disclaimer**

**If the review date of this document has passed please ensure that the version you are using is the most up to date either by contacting the document author or the Governance Directorate.**

**Summary of reviews/amendments**

| Version Number | Date of Review Approved | Date Published | Summary of Amendments |
|---|---|---|---|
| 1 | 22/01/15 | 10/04/15 | This is a new SOP which replaces Reporting Research-Related Adverse Events for Cardiff and Vale UHB Sponsored Clinical Trials of Investigational; Medicinal Products (UHB 180) and Reporting Research-Related Adverse Events in Externally Sponsored Clinical Trials of Investigational; Medicinal Products Hosted by UHB (UHB 181) and encompasses other Safety Reporting Requirements in Clinical Trials of Investigational; Medicinal Products. |
| 2 | 24/04/18 | 03/07/18 | Updated to:<br>• includes reference to forthcoming Legislation<br>• remove reference to Cardiff University Clinical Trials procedures<br>• includes clarifications regarding the reporting of incidents in research and potential serious breaches<br>• includes reference to the UK policy framework for health and social care research<br>• includes information in relation to the MHRA safety reporting update December 2017 |

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| 3 | 28/04/21 | 21/06/2021 | Reviewed and amended to reflect and signpost to updated information on:<br>Clinical Trials legislation<br>Post Brexit MHRA reporting procedures and systems.<br><br>Removal of outdated information<br>Clarifications. |
| 4 | 18/04/2024 | 18/07/2024 | Minimal changes and updates to procedures (will finish this when finalised) |
| 5 | 24/02/2026 | 17/04/2026 | Major updates to make the SOP joint with Cardiff University and to ensure compliance with the new The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 and ICH GCP E6(R3).<br>Approved by JRO QMG on 08.01.26.<br>Approved by JRGG on 24/02/26 |

# Contents

# 1. ABBREVIATIONS AND DEFINITIONS

| | |
|---|---|
| **AE** | Adverse Event |
| **ARSAC** | Administration of Radioactive Substances Advisory Committee |
| **ATMP** | Advanced Therapy Medicinal Products |
| **C&C** | Capacity and Capability |
| **CAG** | Confidentiality Advisory Group |
| **CAVUHB** | Cardiff and Vale University Health Board |
| **CE** | Conformité Européene (CE) |
| **CI** | Chief Investigator |
| **CRO** | Contract Research Organisation |
| **CTIMP** | Clinical Trials of Investigational Medicinal Products |
| **CTU** | Clinical Trials Unit |
| **CU** | Cardiff University |
| **DMP** | Data Management Plan |
| **DSUR** | Development Safety Update Report |
| **EPR** | Early Project Review |
| **GCP** | Good Clinical Practice |
| **HCRW** | Health and Care Research Wales |
| **HRA** | Health Research Authority |
| **IB** | Investigator's Brochure |
| **ICH** | International Conference on Harmonisation |
| **ICSR** | Individual Case Safety Report |
| **IMP** | Investigational Medicinal Product |
| **IMPD** | Investigational Medicinal Product Dossier |
| **IRAS** | Integrated Research Application System |
| **JRO** | (Cardiff) Joint Research Office |
| **MHRA** | Medicines and Healthcare Products Regulatory Agency |
| **MoU** | Memorandum of Understanding |
| **mNCA** | Model Non-commercial Clinical Trial Site Agreement |
| **OID** | Organisation Information Document |
| **PI** | Principal Investigator |
| **PV** | Pharmacovigilance |
| **QMG** | Quality Management Group |
| **QMS** | Quality Management System |
| **RAF** | Risk Assessment Framework |
| **REC** | Research Ethics Committee |
| **R&D** | Research and Development |
| **RSI** | Reference Safety Information |
| **SAP** | Sponsor Assessment Process |
| **SAE** | Serious Adverse Event |

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| **SAR** | Serious Adverse Reaction |
| **SIV** | Site Initiation Visit |
| **SmPC** | Summary of Product Characteristics |
| **SOP** | Standard Operational Procedure |
| **SoE** | Schedule of Events |
| **SoECAT** | Schedule of Events Cost Attribution Template |
| **SSAR** | Suspected Serious Adverse Reaction |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TMF** | Trial Master File |
| **TMG** | Trial Management Group |
| **UKCA** | UK Conformity Assessment |
| **UK-CRC** | UK Clinical Research Collaboration |
| **UKPF** | UK Policy Framework for Health and Social Care Research 2017 (as amended) |
| **USM** | Urgent Safety Measure |

Please read **Appendices A**, **B, C and D** of this SOP alongside the main body of the document.

Technical terms and abbreviations to reflect the language used in the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 and the supporting EU guidance documents (as amended) are used throughout.

In the UK, The Competent Authority is The Medicines and Healthcare Products Regulatory Agency (MHRA). For the purpose of this SOP, the acronym MHRA will be used. However, for international, multicentre trials, this would also mean the relevant Competent Authority in each country, as defined in the trial protocol.

All references to The Clinical Trials Regulations in this document should be taken to mean The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (as amended). All references to ICH Good Clinical Practice (GCP) should be taken to mean the International Council for Harmonisation (ICH) E6 (R3) Guideline for Good Clinical Practice (GCP).

Regulatory compliant definitions of Safety Event, ‘Causality’ and ‘Expectedness’ are included in Appendices B and C.

# 2.0 ROLES AND RESPONSIBILITIES

## 2.1 GENERAL

Pharmacovigilance (PV) is defined as the science of collecting, monitoring, researching, assessing and evaluating information on the adverse effects of medicines, with a view to identifying information about potential new hazards and preventing harm to participants. Robust PV systems are of utmost importance in a CTIMP.

The key points relating to safety reporting and responsibilities are included in Part 6 of The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025.

### 2.1.1 Sponsor Responsibilities

In accordance with the UK Clinical Trial Regulations, the Sponsor has overall responsibility for keeping:

1. 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—

a) in the United Kingdom;

b) conducted outside of the United Kingdom where—

i. the sponsor of both the trial in the United Kingdom and the trial outside of the United Kingdom is the same or, where the sponsor is a company, in the same group, and
ii. the investigational medicinal product being tested or used in the trial conducted outside of the United Kingdom is the same as the investigational medicinal product being tested or used in the clinical trial mentioned in sub-paragraph (a).

2. And for evaluating:

i. the events and reactions mentioned in paragraph (1), with a view to—

a) minimising and preventing any risk presented by the use of the investigational medicinal product to which those events and reactions relate; and

b) taking appropriate measures as soon as reasonably practicable to investigate the risks presented and implement actions for minimising and preventing those risks.

The MHRA has published guidance for the collection, verification and reporting of safety events in clinical trials. This guidance should be read alongside this SOP.

In accordance with the principles of Good Clinical Practice (GCP), the Sponsor may delegate Sponsor functions in a CTIMP to appropriately qualified third parties, teams and individuals. Sponsor oversight of any delegated functions must be upheld and maintained throughout a CTIMP. The Sponsor must ensure that its oversight of CTIMP functions are fit for purpose and proportionate to the risk associated with the CTIMP and that adequate quality assurance and quality control processes are in place to support any delegation of Sponsor functions.

In accordance with the Cardiff Joint Research Office (JRO) SOP for *Applying for Sponsorship of Higher Risk Studies (including Clinical Trials of Investigational Medicinal Products (CTIMPs) and Clinical Trials of Medical Devices (Medical Device Trials))* (SOP-001-05), a UK Registered Clinical Trials Unit (CTU) must be appointed in order for a CTIMP to be eligible for Sponsorship from either CU or CAVUHB.

Responsibility for safety reporting and PV functions in a CU or CAVUHB Sponsored CTIMP must be delegated to a UK Registered CTU or appropriately qualified Clinical Research Organisation (CRO).

CU and CAVUHB cannot act as Sponsor for CTIMPs where it is proposed that responsibility for safety reporting and PV functions are delegated to:

- the JRO or;
- a non UK Registered unit or department or;
- the Chief Investigator (CI) or any other member of the trial management team who does not possess specialist expertise in CTIMP safety reporting and PV.

### 2.2.2 Clinical Trial Unit (CTU)/Clinical Research Organisation (CRO) Responsibilities

For a CTIMP to be eligible for CU or CAVUHB Sponsorship, responsibility for safety reporting and Pharmacovigilance (PV) must be delegated to an appropriately qualified and resourced UK Registered CTU or Clinical Research Organisation (CRO) and this should be confirmed as part of the JRO Early Project Review (EPR) process.

Responsibility for safety reporting and PV will be documented in the Sponsor Delegation of Roles and Responsibilities Memorandum of Understanding (MoU). The MoU is signed by the CI and representatives of the Sponsor and CTU (and other parties, as appropriate) prior to the CTIMP commencing. The MoU is drafted during the CTIMP set-up process and details the internal delegation of Sponsor responsibilities. Please refer to section 5.2 of the Cardiff Joint Research Office (JRO) SOP for *Applying for Sponsorship of Higher Risk Studies (including Clinical Trials of Investigational Medicinal Products (CTIMPs) and Clinical Trials of Medical Devices (Medical Device Trials))* (SOP-001-05) for further information on MoUs.

As a minimum, the following safety reporting and PV responsibilities shall be delegated to a UK Registered CTU in CU or CAVUHB Sponsored CTIMPs and should be set out in the MoU:

- Ensuring that adequate PV information is included in the CTIMP Protocol (see section 3.1 of this SOP);

- Ensuring that an appropriate Quality Management System (QMS) is established within the appointed CTU/CRO which includes adequate SOPs, reporting forms and systems for regulatory compliant safety reporting and safety reviewer training;

- The maintenance of detailed records of all adverse events relating to the CTIMP throughout the duration of the CTIMP and during any follow-up periods (until the End of Trial declaration is submitted for the CTIMP);

- Provision of adequate safety reviewer training for the Chief Investigators (CI) and safety reporting training for any participating site staff (including the Principal Investigators (PIs));

- Responsibility for coordinating and submitting the annual Development Safety Update Report (DSUR) within the required timeframes (see Appendix A of this SOP);

- Reporting of suspected unexpected serious adverse reactions (SUSARs) to the MHRA and REC via the MHRA's Individual Case Safety Report (ICSR) system within the required timelines defined in the UK Clinical Trials Regulations (see Appendix A) and/or in the protocol;

- Reporting requirements for Urgent Safety Measures (USM) to the Sponsor, MHRA and REC (if applicable) (see section 4 of this SOP);

- Ensuring the most up-to-date version(s) of the Reference Safety Information (RSI) for each CTIMP IMP is available at all participating sites;

- Performing an assessment, or coordinating the assessment of, safety events with respect to seriousness, causality and expectedness reported in a CTIMP;

- Ensuring an adequate procedure is in place for the unblinding of CTIMP treatment in accordance with agreed procedures (sometimes referred to as 'emergency unblinding'), where required, before submitting expedited reports to the relevant reporting bodies;

Coordinating the ongoing safety evaluations of any Investigational Medicinal Products (IMPs);Coordination of the safety information for the Clinical Study Report at the end of the CTIMP;

- Any other responsibilities in respect of safety reporting where deemed necessary in accordance with the risk profile of the CTIMP.

### 2.2.3 Investigator (CI and PI) Responsibilities

The CI and PI must ensure that the research team gives priority at all times to the dignity, rights, safety and wellbeing of participants, including carrying out required care following a safety event, and making judgement on the patient's ongoing participation in the trial.

Unless otherwise delegated, CIs and clinical reviewers are responsible for:

- Ensuring compliance with the Protocol and GCP to ensure that reported Serious Adverse Events (SAEs) are valid;
- Expectedness assessments (see Appendix C)
- Causality assessments (See Appendix C). NB. the causality assessment provided by the site PI cannot be downgraded;
- Adhering to CTU/CRO defined SOPs, guidance and training on safety reporting including the provision of prompt responses to queries;
- ensuring the AE log is reviewed regularly. This can be performed by the CI alone or reviewed collectively at regular Trial Management Group (TMG) meetings. These reviews should be documented, in the Trial Master File (TMF).

Unless otherwise delegated, the CI is **also** responsible for:

- Reviewing updates to the Reference Safety Information (RIS) for IMP(s) (which contains the list of expected events) in order to assess the impact on the trial safety profile;
- The literature and safety profile assessment for the annual DSUR;
- The final authorisation of the DSUR prior to its submission.

The Sponsor should ensure that the CI and any other clinical members of staff delegated to undertake clinical safety reviews in a CTIMP receive appropriate training.

#### i. Investigator Safety Reporting Responsibilities in a CU or CAVUHB Sponsored CTIMP

The clinical assessment and classification of any safety event should be undertaken by the CI and/or site PIs. However, this may be formally delegated to another medically qualified member of the research team, as per the Site Delegation Log (SDL). If initial reports are not completed by an investigator (e.g. if they are

completed by the study research nurse) the follow up reports should contain evidence that the assessment decisions were made by a medically qualified doctor. In these circumstances, the SAE form should be reviewed and countersigned by the CI/PI, as per SDL, as soon as possible, afterwards, or in accordance with the protocol.

Responsibility for providing PV and safety review training to the CI and any additional members of staff who are delegated to undertake safety reviews in a CTIMP will be delegated by CU or CAVUHB as Sponsor to the appointed CTU or CRO.

Responsibility for providing safety reporting training to site PIs and relevant site staff is delegated to the CTU/CRO and will be provided during the site initiation training delivered by the CTU/CRO. All site staff with responsibility for safety reporting will be appropriately recorded on the site delegation log. The SDL may be checked during Sponsor, CTU or Host Site monitoring and audits.

Safety reviewing and reporting responsibilities assigned to the CI and site staff should be adequately documented by the CU/CAVUHB Sponsor representative in the MoU for the CTIMP (see section 2.2.2) and in the site agreement between the Sponsor and the Host Site.

### ii. Safety Reporting Responsibilities of organisations providing patient care

NHS Organisations acting as Host Sites in a CTIMP are required to report any safety events to the relevant Sponsor and through their internal systems as appropriate. The requirement to report safety events to the Sponsor's nominated representative (e.g. the appointed CTU or CRO) will be detailed in the site agreement between the Sponsor and the Host NHS site.

Host organisations may have different requirements for internal recording of SAEs and incidents. PIs should ensure they are acting in accordance with these requirements of the Host organisation, in addition to any Sponsor requirements.

### iii. Investigator Safety Reporting Responsibilities in CAVUHB Hosted CTIMPs

The PI or local investigator (as detailed in the Site Delegation Log) will be required to inform the CI and/or the relevant Sponsor of all safety events that occur at their site, following the guidelines and timescales set out in the Clinical Trials Regulations and/or as agreed in the protocol/procedures issued by the Sponsor.
Tasks relating to the management of safety events are commonly delegated to other members of the research team. These must be recorded on the SDL.

## 3.0 SAFETY REPORTING PROCEDURES- PRE-TRIAL PLANNING

### 3.1 Safety Reporting in CU and CAVUHB Sponsored CTIMPs

The arrangements for safety reviewing, reporting and oversight of PV is an important element of the Sponsorship Assessment Process (SAP) and will be discussed early in the trial set-up phase. Sponsor set-up processes for CU and CAVUHB Sponsored CTIMPs will follow the Cardiff Joint Research Office (JRO) SOP for *Applying for Sponsorship of Higher Risk Studies (including Clinical Trials of Investigational Medicinal Products (CTIMPs) and Clinical Trials of Medical Devices (Medical Device Trials))* (SOP-001-05). In accordance with section 5.0 of SOP-001-05, the SAP consists of three stages:

- **Stage 1:** Pre-Funding
- **Stage 2:** Sponsorship in Principle- Permission to Apply for Regulatory and REC Approvals
- **Stage 3:** Trial Set-Up Leading to Final Sponsor Approval to Commence Recruitment

The arrangements for safety reporting and PV will normally be discussed as the grant application is being prepared during Stage 1 of the SAP and at the JRO Early Project Review (EPR) meeting. Confirmation of adequate safety reporting and PV arrangements (i.e. that an accredited CTU or CRO will undertake this work and has been appropriately costed) must be provided by the CI/Research Team at the JRO EPR stage.

Before initiating a clinical trial, the Sponsor should give careful consideration to the following points:

- The specific requirements for recording and notifying adverse events in the trial;
- Which safety events should be recorded and where; and
- Which safety events should be notified to the Sponsor/REC/MHRA and the timelines for notification.

These considerations should take into account the risk profile of the CTIMP and the likely risk to participants, based on what is already known about the IMP(s) and the risk of the trial interventions (confirmed during Stage 2 of the SAP).

During Stage 2 of the SAP, the Sponsor should ensure that the following safety review and reporting arrangements are detailed in the CTIMP Protocol. As a minimum, Protocols for CU and CAVUHB Sponsored CTIMPs should contain the following safety reporting information (in addition to the Protocol requirements of the appointed CTU):

- the standardised definitions of AEs, SAEs, SARs and SUSARs (as per Appendix B of this SOP);
- the safety reporting responsibilities of:

- CTIMP PIs and Sites to the CTU (these responsibilities will also be detailed in the CTIMP Site Agreement with each participating site) and details of where safety events should be recorded (e.g. in the participant's medical records and on the CTIMP Clinical Research Form (CRF)/safety section of the trial database);
- The CTU to the REC and MHRA/relevant Competent Authority;
- The CTU to the Sponsor (in the case of SUSARs and USMs);
- The CTU to the Trial Management Group (TMG (e.g. the presentation of regular line listings of SAEs for review and discussion and the frequency of TMG meetings)

- The contact details for the CTU PV function (including a phone number and email address and any out of hours arrangements);
- information detailing when the recording of AEs and SAEs should commence. NB. safety reporting must start for each participant immediately after they provide their informed consent. Safety reporting for each participant must be performed at least until the end of the systemic exposure to the IMP, though this will be unique to each CTIMP and will depend upon the trial design characteristics and objectives. A written rationale should be provided in case this is not deemed applicable;
- any trial-specific safety reporting requirements (e.g. if any events are considered SAEs in the context of the CTIMP)- this will be determined in accordance with the risk assessment for the CTIMP and the Reference Safety Information (RSI) for the IMP(s). The MHRA guidance for RSIs can be found here.
- any SAEs which would not be considered an SAE in the context of the CTIMP and justification for this;
- information on how causality of SAEs is assessed for the CTIMP;
- information on how expectedness of SAEs is assessed for the CTIMP;
- the process for emergency unblinding (where relevant);
- any particular requirements and considerations with regards to pregnancy reporting (where relevant);
- the process for reporting USM.

Further trial-specific detail on safety reporting may be contained in accompanying CTU support documentation such as Safety Manuals and IMP Management Plans.

The arrangements for PV and safety reporting in a CTIMP will be checked by the JRO Sponsor Representative at Stage 3 of the SAP and prior to issuing Final Sponsor Approval to Commence a CTIMP.

Ongoing monitoring of the CTU/CRO's safety reviewing and reporting processes shall be maintained by the Sponsor throughout the course of a CTIMP through regular attendance at the Trial Management Group (TMG) and through scheduled and triggered Sponsor monitoring and audits of the CTIMP (as detailed in the trial Monitoring Plan).

### 3.2 Safety Reporting in externally Sponsored CTIMPS where CAVUHB is the Host NHS Site

For CAVUHB Hosted CTIMPs, the relevant Sponsor and/or CTU/CRO safety reporting procedures should be adhered to. Sites are usually required to report SAEs to the Sponsor's appointed PV Team within 24 hours of becoming aware of the SAE, unless otherwise stated in the Protocol, CTIMP-specific SOPs or Safety Management Plan. Please refer to Appendix D of this SOP for details on the safety reporting process for CAVUHB Hosted CTIMPs.

It is the responsibility of the CI and site PIs to act in the best interest of the participant at all times and to evaluate the participants' ongoing inclusion in the trial taking any adverse events into consideration.

**For CTIMPs which have been deemed to be high risk by the JRO** (e.g. those involving ATMPs), the local PI (or delegate) is required to submit SAE/SAR/SUSARs recorded at site to the JRO in parallel with reporting to the Sponsor. SAE forms should be emailed to research.governance@wales.nhs.uk. Upon receipt of a SAE/SAR/SUSAR reported to the JRO, JRO staff should check that the relevant Sponsor has also been notified and should confirm this with the PI (or PI's delegate). Any SUSARs reported to the PI by the Sponsor from other sites must also be forwarded to the JRO at the email above.

These requirements will be outlined in the email which confirms C&C. These events will be carefully monitored by the JRO Senior Management Team at routine meetings.

**For CTIMPs deemed to be medium to low risk by the JRO**, it is the responsibility of the local PI to inform the JRO of SUSARs that occur at site in parallel with reporting to the Sponsor. In addition, any concerns regarding safety events concerning a participant, or the ongoing safety profile of the trial should also be reported. The JRO may require information on SAE/SARs for a particular trial following completion of the JRO risk assessment. Instructions on the types of information required and the method of submission will be outlined in the confirmation of C&C email issued to the local PI.

At CAVUHB, SAEs, as defined in the protocol do not require reporting via the Datix system. However, any direct unexpected patient harm must be reported on the CAV Datix system, or local incident reporting system.

Other research related non-compliances, i.e. prescribing or drug administration errors, major drug storage temperature deviations etc should be reported to the Sponsor, as soon as possible after the non-compliance has been identified.

Events which are considered as a potential serious breach of GCP or of the protocol should be reported to the CAVUHB R&D Office in accordance with the CAVUHB SOP

Managing Breaches of Good Clinical Practice or the Study Protocol (UHB 235). The R&D Office will liaise with the research team regarding corrective actions and preventative measures.

## 4.0 URGENT SAFETY MEASURES (USMs).

The Sponsor, delegate or Investigator may implement appropriate and immediate USMs to protect participants against any immediate hazard to their health or safety. Approval is not required before taking these measures. The Sponsor has up to 7 calendar days from receiving notification of any USMs to give written notice to REC and MHRA.

### 4.1 Reporting USM in a CU or CAVUHB Sponsored CTIMP

Responsibility for submitting USM notifications in a CU or CAVUHB Sponsored CTIMP, will be delegated to the appointed CTU/CRO but the CTU should notify the JRO Sponsor contact of any USM implemented in a CTIMP.

If an USM is reported in a CU or CAVUHB Sponsored CTIMP, the JRO Sponsor Representative should record this information on the JRO Risk Register and inform the Clinical Trial Governance Group (CT-GG) at its next meeting. If CAVUHB is also a Host Site in the CTIMP, it may be appropriate to report the details of the USM at the Joint Research Governance Group (JRGG).

The reporting routes for USMs will depend on whether the CTIMP was submitted via the Combined Review approvals process, or via the previous IRAS system (separate REC and MHRA submissions). The notification process should be detailed in the CTU/CRO's respective Safety Reporting SOP.

If the USM requires a modification to the CTIMP, this should be submitted as modification to the Sponsor as soon as possible. The amendment should be marked as being in response to an USM and a copy of the USM notification should be submitted with the modification.

### 4.2 Reporting a USM in a CAVUHB Hosted CTIMP

For CAVUHB Hosted CTIMPs, the CAVUHB Site Team should adhere to the Sponsor's procedures for reporting USMs. Site PIs (or their delegates) are also required to notify the JRO (research.governance@wales.nhs.uk) of any USMs reported in a CAVUHB Hosted CTIMP. It may be appropriate for the JRO to report the details of the USM at the Joint Research Governance Group (JRGG).

## 5.0 PREGNANCY REPORTING IN CTIMPS

Pregnancy or the refusal to take adequate measures to prevent a pregnancy are usually standard exclusion criteria in most (but not all) CTIMPs. Information about

preventing and reporting pregnancies should be given to potential trial participants before they give informed consent. Depending on any known effects of the IMP on spermogenesis, it may also be necessary to monitor the pregnancy of a woman whose male partner is the trial participant.

The pregnancy should be recorded in the participant's medical notes and trial documentation as per protocol and Sponsor requirements.

Where pregnancy is an exclusion criterion, the participant would usually be withdrawn from the trial.

The pregnancy should be followed to termination or to term. In some circumstances, it may be necessary to monitor the development of the newborn for an appropriate period post-delivery. This requirement will be trial-specific and should be documented in the trial risk assessment.

Any congenital anomalies or birth defects, foetal death or spontaneous abortion or any SAE occurring to the mother or neonate should be recorded and reported as an SAE/SAR/SUSAR, as appropriate.

Guidance on the procedure for recording and reporting pregnancy should be included in the trial protocol.

Information regarding pregnancy data provides vital information to the overall knowledge concerning the IMP and is therefore reportable to the Sponsor but not reportable to the regulatory agencies as expedited reports and will be incorporated into the annual DSUR.

Where pregnancy is not an exclusion criterion in a CTIMP, this will be detailed in the CTIMP risk assessment and in the trial Protocol.

### 5.1 Pregnancy reporting in CU and CAVUHB Sponsored CTIMPs

The protocol should contain detailed information regarding pregnancy that is reported for any trial participants and/or their partners, as appropriate. CTUs/CROs appointed in a CU or CAVUHB Sponsored CTIMP should have adequate procedures in place for pregnancy reporting and for the follow-up of pregnancies occurring in a CTIMP participant. A separate pregnancy Participant Information Sheet may be developed for the CTIMP. Pregnancy reporting processes will be checked by the JRO Sponsor representative during Stage 3 of the SAP.

### 5.2 Pregnancy reporting in a Hosted CTIMP at CAVUHB

Provided informed consent is in place, the Principal Investigator (or their delegates) should collect pregnancy information for those who become pregnant while participating in a CTIMP or during a stage where the foetus could have been exposed to the IMP (e.g. if the active substance or one of its metabolites have a long half-life), in accordance with the Sponsor's instructions.

## 6.0 DEVELOPMENT SAFETY UPDATE REPORT (DSUR)

Periodic reporting is important to identify any emerging trends in patient safety. The submission of an annual safety report (known as the Development Safety Update Report, or DSUR) is a condition of the ongoing Clinical Trial Authorisation (CTA) for a CTIMP.

The DSUR must be submitted by the Sponsor to the MHRA within 60 days of the 'birth date' of the CTA (i.e. the date the CTA was originally issued by the MHRA). Note that the 'birth date' of the CTA is not usually the same date as the date the trial is opened to recruitment. A definition of the timelines for submitting a DSUR are included in Appendix A of this SOP. The DSUR should include all new available safety information received during the reporting period.

The RSI (IB or SmPC) in place at the start of DSUR reporting period should be appended to the DSUR. Where the RSI has been revised during the DSUR reporting period, the current version should also be submitted with the DSUR. The DSUR should include date and version number of the IB or SmPC.

The DSUR should include:

- an analysis of the participants' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk/benefit;
- a line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the trial(s), including all SUSARs from third countries;
- an aggregate summary tabulation of SUSARs that occurred in the concerned trial(s).

Full details of what to include in a DSUR can be found in the ICH E2F guidance.

If a CI is conducting more than one trial using the same IMP, one DSUR should be submitted for the IMP, rather than submitting individual reports for each trial including that IMP. An online payment for the DSUR must be made to the MHRA by credit card prior to the DSUR submission via the MHRA DSUR portal. Current MHRA fees for the DSUR submission may be found here. Guidance on how to make the DSUR submission payment to the MHRA may be found here. Receipt of payment must be uploaded as part of the DSUR submission. DSURs submitted without prior payment will be considered invalid by the MHRA.

The DSUR submission should include:

- a cover letter,
- The completed DSUR,
- the emailed receipt confirming that the fee has been paid.

The cover letter must include:

- a listing of all the IRAS IDs and EudraCT numbers of trials covered by the DSUR
- an email address for correspondence
- the payment reference number in the format: 'DSUR-[5 digit MHRA company number]-[IMP name]-[Payment date DD/MM/YYYY]'

**i. For CTIMPs submitted via the Combined Review IRAS system**

If at least one of the trials covered by the DSUR has gone through the Combined Review process, then the report should be submitted directly via the Combined Integrated Research Application System (IRAS). Further information can be found on the Health Research Authority (HRA) website.

**ii. For CTIMPs submitted via the previous IRAS system (separate REC and MHRA submission)**

DSURs should be submitted using MHRA Submissions via the Human Medicines Tile. Please select 'Development Safety Update Report' as the Regulatory Activity and 'Original Submission' from the Regulatory sub activity dropdown list. Acknowledgements of receipt for DSUR submissions are generated by MHRA Submissions where a confirmation of submission is emailed to the reporter.

At the end of the DSUR reporting period the Sponsor may assess the new safety information that has been generated and submit any proposed safety changes to the Investigator's Brochure as a modification. This modification must be supported by the DSUR and approved before the reference safety information (RSI) is changed.

### 6.1 DSUR submissions in CU and CAVUHB Sponsored CTIMPs

Responsibility for preparing and submitting the DSUR in a CU and CAVUHB Sponsored CTIMP is delegated to the appointed CTU or CRO (in liaison with the CI). Adequate funds to cover the annual cost of the DSUR submission for the projected lifetime of the CTIMP should be costed into the funding for the CTIMP by the CTU/CRO.

### 6.2 DSUR submissions in CAVUHB Hosted CTIMPs

The submission of the DSUR for a CTIMP Hosted at CAVUHB should be in accordance with the instructions provided by the CTIMP Sponsor.

Further information on routine safety and progress reporting requirements, and the content and submission of DSURs can be found in UHB 406 *Reporting and Transparency Requirements for CAVUHB and CU Sponsored Research* SOP. Documents are available upon request from the JRO Office.

## 7.0 DISSEMINATION AND TRAINING

SOPs are reviewed by the JRO Quality Management Group (QMG) and presented to the JRGG and the joint Clinical Trial Governance Group (CT-GG) where relevant. Once approved, they are published on the CAVUHB Intranet and sent to the R&D Leads to disseminate appropriately. The Clinical Board R&D Leads should facilitate implementation by ensuring that all relevant research active personnel within their Boards are aware of the Procedure and the implications for their practice. Education and support should be available from the JRO for researchers who are involved in conducting clinical research studies.

## 8.0 ELECTRONIC REFERENCES AND RESOURCES

The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025:
https://www.legislation.gov.uk/uksi/2025/538/part/6

Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')
https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2011:172:0001:0013:EN:PDF

Guidance for the reference safety information (RSI) for clinical trials, updated to include UK specific clarifications.
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#reference-safety-information--updated-guidance

MHRA Blog on Reference Safety Information (RSI) for Clinical Trials – MHRA Inspectorate

MHRA Safety Reporting web pages
https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues

HRA safety reporting web pages. Safety reporting - Health Research Authority

MHRA Guidance on submitting clinical trial safety reports and Individual Case Safety Reports (ICSR).
https://www.gov.uk/guidance/guidance-on-submitting-clinical-trial-safety-reports#reporting-susars-using-the-new-reporting-routes

EU Guidance on Investigational Medicinal Products (IMPs) and Non Investigational Products (NIMPs)
https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:082:0001:0019:en:PDF

MHRA Submissions via the Human Medicines Tile.
https://www.gov.uk/guidance/register-to-make-submissions-to-the-mhra

ICH E2F guidance - DSURs.
https://database.ich.org/sites/default/files/E2F_Guideline.pdf
*ICH_E6(R3)_Step4_FinalGuideline_2025_0106.pdf- Safety Assessment and Reporting (section 3.13)*

HRA CTIMPs Safety Report information
https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

# Appendix A: UK REGULATORY SAFETY REPORTING TIMELINES

## i. Suspected Unexpected Serious Adverse Events (SUSARS)- notification requirements

Regulation 25 of The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 defines the reporting timelines for SUSARs as follows:

(1) A sponsor shall ensure that all relevant information about a suspected unexpected serious adverse reaction which occurs during the course of a clinical trial in the United Kingdom and is fatal or life-threatening is reported as soon as possible to the licensing authority, and in any event no later than **7 days** after the sponsor was first aware of the reaction;

(2) A sponsor shall ensure that a suspected unexpected serious adverse reaction which occurs during the course of a clinical trial in the United Kingdom, other than those referred to in paragraph (1), is reported as soon as possible to the licensing authority, and in any event no later than **15 days** after the sponsor is first aware of the reaction.

## ii. MHRA reporting requirements for the DSUR submission

Regulation 26 of The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 defines the timelines for the submission of the Development Safety Update Report (DSUR) as follows:

(1) Within the period of **60 days** beginning with the day after the day on which the reporting year ends, a sponsor shall, in relation to each investigational medicinal product tested in clinical trials referred to in regulation A32(1), provide the licensing authority with a report on the safety of the participants of those trials.

## Appendix B: Safety Reporting Definitions

### DEFINITIONS

Directive 2001/20/EC, Article 2, lists definitions of terms. The following has been adapted from the Clinical Trials Regulations:

| **Pharmacovigilance** |
|---|
| Pharmacovigilance in CTIMPs is the science of collecting, monitoring, researching, assessing and evaluating information on the adverse events of medicines, including placebos, with a view to identifying information about potential new hazards and preventing harm to participants |

| **Adverse Event (AE)** |
|---|
| Any untoward medical occurrence in a patient or clinical trial participant administered an Investigational Medicinal Product (IMP) and which does not necessarily have a causal relationship with this treatment.<br>Therefore an AE can be any unfavourable or unintended sign, symptom including laboratory data, in a participant to whom an IMP has been administered, including occurrences which are not necessarily caused by or related to that product |

| **Adverse Reaction (AR)** |
|---|
| All untoward and unintended responses to an IMP related to any dose administered<br>Comment: All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product would qualify as adverse reactions. The expression ‘reasonable causal relationship’ means to convey, in general, that there is evidence or argument to suggest a causal relationship |

| **Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR)** |
|---|
| Any AE or AR that at any dose:<br>- results in death<br>- is life-threatening*<br>- requires hospitalisation or prolongation of existing hospitalisation<br>- results in persistent or significant disability or incapacity<br>- consists of a congenital anomaly or birth defect<br><br>Comment: Medical judgement should be exercised in deciding whether an adverse event/reaction should be classified as 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above may also be considered serious.<br>*Life-threatening in the definition of a serious adverse event or serious adverse reaction 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. |

| **Unexpected Adverse Reaction (UAR)** |
|---|
| An adverse reaction, the nature or severity of which is not consistent with the applicable product information (RSI) |

| **Suspected Serious Adverse Reaction (SSAR)** |
|---|
| An adverse reaction, the nature or severity of which is not consistent with the applicable product information (RSI) |

| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** |
|---|
| An adverse reaction that is classified in nature as both serious and unexpected |

## Appendix C: Adverse Event Assessment Guide

### (1) SERIOUSNESS

An event is considered serious if it meets one or more of the following criteria:

- Results in death; - Is life threatening*;
- Requires hospitalisation or prolongation of existing hospitalisation**;
- Results in persistent or significant disability or incapacity; - Consists of a congenital anomaly or birth defect***.

* It is not an SAE if the prolongation of hospitalisation relates to non-medical fitness for discharge

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the participants death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

### (2) CAUSALITY

The relationship between the drug/device/procedure and the occurrence of each adverse event should be assessed and categorised as below. The Investigator should use clinical judgement to determine the relationship. Alternative causes, such as natural historical events of the underlying diseases, concomitant therapy, other risk factors etc, will also be considered. The Investigator should also consult the SmPC or IB as appropriate. All adverse events judged as having a reasonable suspected causal relationship to the IMP are considered to be adverse reactions. The expression 'reasonable suspected causal relationship' is meant to convey in general that there is reason (e.g. facts, evidence or arguments) to suggest a causal relationship.

| | |
|---|---|
| **NOT RELATED** | Temporal relationship of the onset of the AE, relative to the administration of the product, is not reasonable or another cause can explain the occurrence |
| **UNLIKELY** | Temporal relationship of the onset of the AE, relative to the administration of the product, is likely to have another cause which can by itself explain the occurrence |

| | |
|---|---|
| **POSSIBLY RELATED*** | Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause |
| **PROBABLY RELATED*** | Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and the event is more likely to be explained by the product than any other cause |
| **DEFINITELY RELATED*** | Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive |

*Note: Where an event is assessed as possibly, probably or definitely related, the event is an adverse reaction

### (3) EXPECTEDNESS

Adverse reactions must be considered as unexpected if they add significant information on the specificity or severity of an expected adverse reaction. The expectedness of an adverse reaction shall be determined according to the reference documents as defined in the clinical trial protocol (e.g. IB or SmPC)

| | |
|---|---|
| **EXPECTED** | Reaction previously identified and described in protocol and/or reference documents |
| **UNEXPECTED** | Reaction not previously described in the protocol of reference documents |

NOTE: The protocol must identify the reference documentation used

## Appendix D: ADVERSE EVENT RECORDING AND REPORTING PROCEDURE AND TIMELINES FOR CAVUHB HOSTED CTIMPS

| 1. RECORD | 2. ASSESS | 3. REPORT |
|---|---|---|

**Step 1: Record**

The CI/PI or delegated member of the research team must review all documentation, including Case Report Forms (CRFs) and source documents
(hospital notes, laboratory and diagnostic reports) relevant to the safety event.

The trial protocol should be consulted to see whether the safety event is disease-related. Unless the protocol states otherwise, all safety events including non-serious AEs should be recorded, consistent with the purpose of the trial and any toxicity and efficacy endpoints.

The safety event should be recorded in participants ' medical notes, worksheets and/or a CRF as stipulated in the protocol. All available information should be recorded for analysis at a later stage and for inclusion in any reports.

**Step 2: Assess**
Adverse events should undergo three main assessments to enable classification

- Assessment of Seriousness
- Assessment of Causality Assessment of Expectedness

The Adverse Event Assessment Guide **(Appendix C)** provides guidance on safety event assessment and classification.

The assessment should be undertaken by the CI/PI or medically qualified delegate. This should be outlined in the protocol and recorded on the SDL.

For multi-sites trials a CI cannot downgrade a PI's assessment of an event but the CI/ Sponsor may upgrade an event if it is judged necessary.

In blinded trials involving a placebo and active drug, the factors in **Appendix C** should be evaluated on the basis that the participant was on the active drug.

In blinded trials involving two active drugs, the person responsible for assessment may be able to state that if the participant were on drug 'A', the event would be causal and/or unexpected, but if on drug 'B' it would be expected.

Where the event is believed to be a SUSAR, then the trial may need to be unblinded depending on the circumstances (see Section 4.0 below).

**Step 3: Report**

Reports should be sent to the relevant bodies depending on the nature of the safety event. These are as follows:

| | Sponsor (or Delegate) | CI | MHRA | REC |
|---|---|---|---|---|
| **AE/AR** | ✓ | | | |
| **SAE/SAR** | ✓ | ✓ | | |
| **SSAR** | ✓ | ✓ | | |
| **SUSAR** | ✓ | ✓ | ✓ | |

**Adverse Events (AEs) & Adverse Reactions (ARs)**

Where an AE/AR is identified in the protocol as critical to the evaluation of the safety of the trial, then they must be reported to the Sponsor.

For all other AE/ARs, except where the protocol states otherwise, these should be recorded in detail in the participant medical notes or other source data, and on a case record form or equivalent, as per Sponsor requirements.

**Serious Adverse Events (SAEs) & Serious Adverse Reactions (SARs)**

Reports of SAEs/SARs must be notified, to the relevant bodies (as per table above) within **24 hours** from the point a safety event has been assessed as an SAE/SAR (other than those identified in the protocol as not requiring immediate reporting).

An initial report may be made orally but must be followed up as soon as is practically possible with a written report on the SAE/SAR report form, or as stipulated in the protocol, including an assessment of seriousness. Information not available at the time (such as test results) must be forwarded once available.

## Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs must be reported to the Sponsor immediately, using the Sponsor's report form or as stipulated in the protocol.

All SUSARs must be reported to the MHRA by the Sponsor or delegate, via the relevant MHRA reporting system, in an unblinded state. Following Brexit, there have been some changes in reporting systems. Sponsors and Contract Research Organisations (CROs) must register to either the Individual Case Safety Reports (ICSR) Submissions or the MHRA Gateway to enable configuration of their systems in order to submit SUSARs to the MHRA. Latest information on reporting SUSARs using the new operating systems and instructions for registering has been published at MHRA Guidance on submitting clinical trial safety reports. This information may be updated, so it is important to refer to the latest information on the Managing your Authorisation section of the Managing Your Authorisation pages of the MHRA website to ascertain the appropriate system for individual trials. The trial protocol should contain instructions on unblinding, and these instructions should be followed.

The Sponsor or delegate is required to ensure that the investigators responsible for the conduct of a trial are informed of any SUSARs that occur. No timelines are specified in the regulations for reporting to investigators; however, this should be done in a timely manner to ensure investigators are kept fully informed of all safety information.

## Fatal or Life-threatening SUSARs

The Sponsor or delegate must inform the relevant bodies as soon as possible but no later than **7 calendar days** after the Sponsor first has knowledge of a reaction which requires expedited reporting. Any further information should be forwarded to these bodies within an additional **8 calendar days**.

## Non-fatal or Non life-threatening SUSARs

The Sponsor or delegate must inform the relevant bodies as soon as possible but no later than **15 calendar days** after they first have knowledge of a reaction which requires expedited reporting. Follow up information should be sent within 15 days of the Sponsor having knowledge of the information. If significant new information on an already reported case is received by the Sponsor, the clock starts again at day zero, i.e. the date of receipt of new information. This information should be reported as a follow-up report within 15 days (or 7 days for fatal/life threatening events.).

## SUSARs Associated with Non-IMP/IMP Interactions

A Non Investigational Medicinal Product (NIMP) is a medicinal product which is not classed as an IMP in a trial, but may be taken by participants during the trial.

Examples include concomitant or rescue/escape medication used for preventive, diagnostic or therapeutic reasons and/or medication given to ensure that adequate medical care is provided for the participant during a trial. See EU Guidance on Investigational Medicinal Products (IMPs) and Non Investigational Products (NIMPs) SUSARs that result from a possible interaction between an IMP and a NIMP, (i.e. the reaction cannot clearly be attributed to the NIMP alone) should also be reported as above.

**Minimum Reporting Requirements for SUSARs**

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits set out in the Clinical Trials Regulations, when the following minimum criteria are met:

- A suspected investigational medicinal product;
- An identifier for the participant (e.g. trial number);
- An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship;
- An identifiable reporting source;

And, when available and applicable:

- The IRAS ID and/or a EudraCT number (or, in the case of non-European community trials, the

Sponsor's trial protocol code number); and

- A unique case identification (i.e. Sponsor's/CTUs case identification number)
- Treatment assignment after unblinding and validation (or not) of the suspected causes.

The Sponsor is responsible for ensuring that all relevant follow-up information is requested and submitted to MHRA and REC as appropriate.

For multi-site EU trials, Sponsors should ensure the latest guidance on the MHRA website is followed, to ensure appropriate safety reporting.

## Appendix E: Flowchart