Recording, Managing and Reporting Adverse Events in the UK

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Version	Date	Reason for Change
Version 1.0	03 Jul 2006	Non-IMP SAE clarification and updated instructions from NRES and MHRA
Version 2.0	25 Jun 2007	Annual review
Version 3.0	26 Jun 2008	Formation of Joint Research Office. Recommended additions following MHRA inspection.
Version 4.0	08 Feb 2010	Content review and addition of controlled document statement
Version 5.0	14 Jul 2011	Annual Review and addition of e-SUSAR reporting process
Version 6.0	29 Nov 2012	Annual Review
Version 7.0	18 Feb 2015	Scheduled Review
Version 8.0	25 Oct 2017	Scheduled Review
Version 9.0	29 Aug 2018	Updated to address the MHRA inspection findings
Version 10.0	19 Oct 2020	Scheduled Review Templates removed and administrative changes JRCO name change to RGIT.
Version 11.0	03 Nov 2020	Safety reporting update
Version 12.0	13 Jan 2021	Amendments due to leaving the European Union from 1st January 2021.
Version 13.0	06 Feb 2024	Scheduled Review
Version 14.0	27 Apr 2026	Updates following legislative changes

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1. PURPOSE

This SOP describes the process for recording, managing and reporting adverse events for Imperial College sponsored studies of both Investigational Medicinal Products (IMPs) and non-IMPs in the UK, but the principles are relevant for all clinical trials.

2. INTRODUCTION

It is essential that all adverse events which occur during study participants' involvement in a research project are recorded and reported in order to ensure their continuing safety.

The Medicines for Human Use (Clinical Trials) Regulations 2004 ("the Clinical Trials Regulations"), as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 and the Department of Health's Research Governance Framework for Health and Social Care, set out specific requirements for the managing of adverse events (AE). Of importance, is the assessment of any event for **causality** and **expectedness**.

AEs can be classified into different categories (further information given in section 2.1):

1. Adverse Event
2. Adverse Reaction
3. Serious Adverse Event/Reaction
4. Suspected Serious Adverse Reaction
5. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Each type of AE is subject to different reporting requirements. It is important that this SOP is followed as 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 being carried out by the Chief Investigator (CI) or Principal Investigator (PI).

2.1 DEFINITIONS

2.1.1. 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 AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

2.1.2. 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". This 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.

2.1.3. Serious Adverse Event/Reaction (SAE/SAR)

All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to the IMP (see above as to what constitutes a "reasonable causal relationship") and qualify as "serious".

A serious safety event (e.g. 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 at any dose:

- 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
- other important medical event (medical events which may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences)

SAEs include all serious events independent of whether they have a suspected causal relationship to the investigational medicinal product (IMP) or not. Medical judgement should be exercised in deciding whether an adverse event/reaction is serious.

Life-threatening, in the definition of an SAE or SAR, refers to an event in which the subject was at risk of death at the time of event. It does not refer to an event which hypothetically might have caused death if it were more severe.

In general, hospitalisation means that the participant has been admitted to the hospital for inpatient care, for example to an inpatient ward or to an emergency department for observation and/or treatment (usually involving at least an overnight stay), that would not have been appropriate in the physician's office or outpatient setting. The protocol should clarify what is considered as hospitalisation in the context of the trial setting since this may vary depending on the overall risk assessment for the trial. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is generally not considered an SAE.

Pregnancy does not meet the definition of an SAE. However, should a study participant become pregnant whilst undertaking a clinical trial of an investigational medicinal product (CTIMP), or aid in the conception of a child whilst they are participating in a CTIMP, the pregnancy and resulting child should be followed up for a period of no less than 18 months to verify whether a congenital anomaly or birth defect is present. This will be subject to guidance from the relevant pharmaceutical company. Pregnancies

and outcome will be included in the Annual Safety Reports. The Chief Investigator (CI) will report any pregnancy occurring on a Clinical trial via the SAE form to the RGIT.

'Serious' and 'severe' are not synonymous:

- **Severity**: Refers to the intensity of a specific event and is often classified by its effect on the everyday living of the participant as mild, moderate or severe.

Severity is not the same as "serious", which is based on patient/event outcome or action criteria of an AE or AR and serves as a guide for defining regulatory reporting.

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).

2.1.4. Suspected Serious Adverse Reaction (SSAR)

Any adverse reaction that is classed as serious and which is consistent with the information about the IMP listed in the Summary of Product Characteristics (SmPC) or Investigator Brochure (IB). For SARs, the determination of **expectedness** should use the latest approved version of the RSI at the moment of occurrence of the event applies **for each IMP used in the trial**, not the RSI at the time of case receipt by the sponsor. For IMPs used within their Marketing Authorisation (MA), the SmPC must be in the Trial Master File (TMF) and provided to the clinical trial pharmacist. In the scenario where an IMP has a MA, but the MA holder also has an IB available for that IMP, then either document can be used as the RSI but must be justified. Once either an SmPC or IB has been selected as containing the RSI to be used for the trial, then only that document must be included in applications and updates must only be provided using the same document type .The CI is responsible for ensuring the SmPC or IB is reviewed at least annually (recommended to be completed at the time of the annual DSUR) and any changes to the Reference Safety information (RSI) should be notified to the clinical trial pharmacist. Current SmPCs can be accessed at Electronic Medicines Compendium (EMC) (*cited on 03 Dec 2023*).

The location of the RSI should be clear. It should also be clear that the RSI has been authorised by the licensing authority, either as part of the initial application or via a subsequent substantial modification. The current version of the RSI document must be specifically distributed to all who require it to ensure the same version is used by all required PIs, particularly if the RSI is in an SmPC. It is not acceptable to direct an investigator to a website where multiple versions are available or where a more recent but unauthorised version is available.

2.1.5. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse reaction that is classed as serious and is suspected to be caused by the IMP that is **not** consistent with the information about the IMP in either the SmPC or IB (i.e. it is suspected and unexpected). The RSI includes a list of medical events defining which reactions are expected for the IMP being administered to clinical trial subjects and therefore do not require expedited reporting to the Competent Authority. Each serious adverse event that occurs in terms of expectedness (for each IMP used in the trial) should be reviewed against the RSI. If the event is not listed as expected or has

occurred in a more serious form than anticipated, this should be considered a SUSAR. For reactions to be excluded from expedited regulatory reporting they must be listed in the RSI or clearly defined in the current approved version of the protocol. Any change to the RSI is a change to the Risk/Benefit and requires a substantial modification be submitted and approved by the MHRA before it is implemented in the trial. It is the CI's responsibility to ensure the modification is submitted to the MHRA. Only then an updated SmPC/IB should be added to the TMF and used by the CI/PI as reference for safety reporting (SUSARs).

Fatal SARs should usually be considered unexpected even if previous fatal SARs have occurred and would therefore be SUSARs. Fatal SARs can only be considered expected for IMPs with a marketing authorisation (MA) when it is clearly stated in the table or list of ARs in section 4.8 of Summary of Product Characteristics (SmPC) that the IMP can cause these fatal SARs, and where that SmPC is submitted as the RSI for the trial.

If there are expected life-threatening or fatal SARs listed in the RSI section of an IB, the RSI should include the number of suspected life-threatening and fatal suspected SARs that have occurred. These data should be provided in separate columns. If a fatal and/or a life-threatening SAR is added to the RSI section of an IB, an update to the benefit/risk statement for clinical trial participants should be provided and adequate risk minimisation measures should be proposed in an updated clinical trial protocol.

3. RESPONSIBILITIES

There are several responsibilities when managing adverse events. Below is a list of responsibilities for both the Investigator and the Sponsor (for Imperial College sponsored studies).

The CI has overall responsibility for the conduct of the study. In a multi-site study, the CI has co-ordinating responsibility for reporting adverse events to the Medicines and Healthcare products Regulatory Agency (MHRA).

The Principal Investigator (PI) has responsibility for the research at a local site where the study involves specified procedures requiring site-specific assessment. There should be one PI for each research site. In the case of a single-site study, the CI and the PI should be the same person. The PI is responsible for informing the CI, or the coordinating research team, of all adverse events that occur at their site following the guidelines below.

Any CI/PI who has agreed to undertake duties for pharmacovigilance delegated by the Sponsor must undertake both Investigator's and Sponsor's responsibilities as described throughout this document.

3.1.1 Investigator's Responsibilities

1. PI to report all SAEs and SUSARs within agreed timelines to the CI.
2. CI to report all SAEs within agreed timelines to the Sponsor.
3. CI to report SUSARs within agreed timelines to the Sponsor, MHRA & other relevant parties.
4. CI to provide the Sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety within the agreed timeframes specified in the protocol.
5. PI & CI to assess each event for seriousness, causality & expectedness.
6. CI to supply the Sponsor, MHRA, and relevant NHS Trust R&D with any supplementary information they request.

3.1.2 Sponsor's Responsibilities

The Sponsor retains ultimate responsibility for the safety of trial participants and for compliance with regulatory requirements, even where operational activities are delegated to the Chief Investigator or other parties.

1. *Ongoing safety evaluation of any IMP(s), including trend analyses.
2. *Promptly notify all Investigators and MHRA, of any findings that may affect the health of subjects. This may include informing investigators using the same IMP in different studies.
3. *Keep detailed written reports of all AEs reported by PIs and performing an evaluation with respect to seriousness, causality and expectedness.
4. *Report all relevant safety information to the relevant REC and MHRA.
5. *Report all SUSARs to the MHRA and Marketing Authorisation (MA) holder(s), within given timelines. Investigators do not need to be informed of SUSARs but the CI may wish to notify investigators of the occurrence through a "Dear Investigator" letter or an updated Investigator's Brochure (IB).
6. *Break treatment codes before submitting expedited reports to MHRA for specific subjects, even if the Investigator has not broken the code. (**Note**: A system for maintaining blinding for the CI/PI and trial staff may need to be agreed in advance).
7. *Submit the annual safety report to Sponsor and MHRA
8. Encourage the setup of Independent Data Monitoring Committees (IDMC) for phase III clinical trials that have high morbidity/mortality and describe their function in the protocol.
9. Ensure written SOPs and systems are in place to ensure quality standards and contractual agreements are met.
10. Ensure that personnel responsible for pharmacovigilance activities are registered and authorised to access all relevant regulatory safety reporting systems required for the conduct of the trial, including MHRA systems for UK reporting (e.g. ICSR portal) and, where applicable, European Medicines Agency (EMA) systems for trials conducted in EU Member States.

*Note: Where Imperial College AHSC is Sponsor for a study, responsibilities 1-7 are delegated to the Chief Investigator. Correspondence for Imperial College AHSC sponsored studies should be sent to the Research Governance and Integrity Team (RGIT).

The Sponsor must ensure that appropriate systems are in place for:

- continuous safety surveillance of investigational medicinal products
- pharmacovigilance data management and safety reporting
- detection and evaluation of emerging safety signals
- oversight of delegated safety reporting activities.

Where responsibilities are delegated to the Chief Investigator or trial team, the Sponsor must maintain documented oversight through:

- formal delegation agreements
- periodic review of safety data
- monitoring of reporting compliance.

The Sponsor must ensure that all suspected unexpected serious adverse reactions (SUSARs) and other relevant safety information are reported to the appropriate regulatory authorities within the required timelines.

3.2 Pharmacovigilance System

The Sponsor must maintain a pharmacovigilance (PV) system appropriate to the scale and risk profile of the clinical trials sponsored.

The PV system must ensure:

- collection and documentation of safety information
- evaluation of adverse events for seriousness, causality and expectedness
- detection of safety signals
- compliance with regulatory reporting requirements.

4. PROCEDURES

4.1 STUDY PLANNING

All protocols should list where known side effects and adverse reactions contained within the manufacturer's product information can be located (e.g. RSI). This should be written in agreement with the relevant drug/device company where applicable. Rare/very rare events may or may not be included depending on individual study requirements.

A detailed explanation of SAE reporting procedures should be included in the protocol. AEs and SAEs should be recorded by the sponsor and the investigator for each participant from the signature of informed consent, unless specified otherwise in the protocol.

A generic SAE reporting form is available in Appendix 1 RGIT_TEMP_003, please refer to the SOP, Associated Documents & Templates page (*cited on 04 Dec 2023*).

4.1.1 Which AE to Record?

The CI can decide how to record and report adverse events, whether expected or not. Adverse events are usually described on case report forms (CRFs), unless they are

classified as serious, in which case, these should be reported on a specific SAE form (see Appendix 1 RGIT_TEMP_003 for an example). It should be clearly stated in the study protocol and the local SOP what will be recorded and how the reporting is to be managed.

It may be decided that all, or only some, non-serious AEs are to be recorded. Whatever option is chosen, it must be consistent with the purpose of the trial and any toxicity and efficacy end points.

4.1.2 Which SAEs to Report?

The management and reporting arrangements for SAEs should be in place for all trials. Agreements at the beginning of the trial should be made for such SAEs that can be defined as disease-related and therefore not subject to expedited reporting. The procedures for managing and reporting SAEs must be clearly defined in the protocol.

It is recommended that an Independent Data Monitoring Committee (IDMC) is appointed in order to review safety data regularly throughout the trial and when necessary, recommend to the Sponsor whether to continue, modify or terminate the trial. Again, this procedure must be defined in the protocol.

As with all recording and reporting, subject confidentiality and adherence to the Data Protection Act (2018) must be maintained on all reports.

Safety recording and reporting in lower risk trials (for example those which the risk is no greater than standard of care, as evaluated in a risk assessment) can be simplified from what is described in this SOP, applying a risk proportionate approach (please refer to RGIT_Temp_082 which can be completed for low risk trials to see if they meet the criteria for reduced safety reporting). Risk adaptations to safety reporting refer to documenting of AEs in source documents, recording of AEs in the case report forms (and hence reporting to the sponsor) and to the requirements of immediate (not later than within 24 hours of obtaining knowledge of the event) reporting (of SAEs/SUSARs) by the investigator to the sponsor. Any such adaptation should be clearly stated and justified in the protocol.

5. DURING THE TRIAL

AEs, including SAEs, should be recorded by the sponsor and the investigator from the signature of informed consent to the end of the trial, unless otherwise provided for in the protocol. For example, where obtaining consent is delayed due to the nature of the trial (such as those in emergency medicine scenarios), safety reporting should commence from the enrolment of the participant, which should be explicitly defined in the protocol.

Each AE must be evaluated for **seriousness**2.1.3**, causality and expectedness (for each IMP used in the trial)**. The responsibility for this evaluation can be shared between the CI, PIs and trial teams for the expectedness evaluation, where specific sponsor delegation, appropriate procedures and staff training are in place and documented. It is best practice for the treating PI at each local site to evaluate each event, before reporting it to the CI. It must be stated in the clinical trial protocol and the

local SOP who will take responsibility for the assessment and reporting of such events to the Sponsor and CI simultaneously. As expedited reporting may be required, this SOP assumes that responsibility of initial assessment and reporting to the CI lies with the PI.

All reported AEs should be named as per the most appropriate "Preferred Term" located within the latest version of the coding dictionary being used in the trial (e.g. MedDRA).

Flowcharts in Appendix 2 RGIT_TEMP_004 are designed to enable Investigators/research personnel to assess AEs and SAEs should they occur during the trial and decide if the event requires further expedited reporting by the CI.

5.1 CAUSALITY

All adverse reactions should be assessed for causality by a trained medical professional within the study team (if not the PI, the staff member must be delegated this responsibility by the PI on the delegation log). The definitions below can be used:

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible*	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable*	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely*	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

***For AEs that are considered serious and unexpected; if the relationship is defined as possible, probable or definitely related, these AEs should be notified to the MHRA and Sponsor as SUSARS.**

In case of ARs assessed as 'unknown' or 'not assessable' for which the investigator cannot make a decision with regards to relatedness to the IMP, the CI, as delegated by the Sponsor, should consult the reporting investigator and encourage him/her to express an opinion. If (despite all efforts) the causality assessment cannot be made by the investigator, SAEs should be considered to be related to the IMP and reported as SUSARs (if they are not listed as an expected SAR in the RSI).

If different causality definitions are specified in the protocol, it must be clear which definitions constitute a 'related' event.

The causality assessment given by the principal investigator should not be downgraded by the sponsor or chief investigator. If the sponsor or chief investigator disagrees with the principal investigator's causality assessment, the opinion of both the principal investigator and the sponsor/chief investigator should be provided with the report.

5.2 NIMPs

In cases of a suspected interaction of a non-IMP with the IMP, the reporting rules for the IMP apply.

Safety reporting (referring to all adverse reactions) with regards to authorised non-IMPs should be made in accordance with post-marketing requirements for that non-IMP, irrespective if they are used in accordance with the terms of the marketing authorisations of these products. It should be noted that investigators and sponsors are encouraged to report suspected adverse reactions to the non-IMP to MHRA (via the Yellow Card Scheme) or to the marketing authorisation holder.

Safety of non-authorised non-IMPs (that should be used only exceptionally in clinical trials) should be reported in the same way as IMPs. Accordingly, SARs related to non-authorised non-IMPs should all be considered as SUSARs and should be reported to the licensing authority. If any adverse reaction associated with the non-IMP is likely to affect the safety of the trial participants, the sponsor should take any appropriate actions, including an urgent safety measure, as applicable.

Where an adverse event occurs that, following a causality assessment, is suspected to be related to a NIMP only, the requirements per regulation 32 of the Clinical Trials Regulations still apply.

5.3 REPORTING GUIDELINES: CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS (CTIMP)

Once the CI/PI has evaluated the AE in terms of seriousness, causality and expectedness (**for each IMP used in the trial**), the following guidelines should be followed.

5.3.1 AEs

AEs that are not considered serious should be included in the patient notes and on the relevant case report forms (CRFs). The completed form should be filed along with the other CRFs for the study and a copy provided to the Sponsor as agreed.

5.3.2 SAE

If the AE is assessed as serious, the PI **must** report the event to the CI and sponsor **immediately or within 24 hours** of being made aware of the event (other than those SAEs identified in the protocol as not requiring immediate reporting).

The PI/CI must send all SAE reports to the Research Governance and Integrity Team, Imperial College AHSC immediately or within 24 hours after becoming aware of the event at the below address: rgit.ctimp.team@imperial.ac.uk
The initial report can be made verbally but must be promptly followed with a detailed, written report. The PI must record the event with his assessment of seriousness, (along with causality, expectedness and severity) on a trial SAE form provided by the CI (see Appendix 1). The PI should ensure that any follow-up information is provided when available. **Where supporting documents are sent with this form, these must be anonymised/pseudonymised.** Where the information available is incomplete at that time, as much information as can be ascertained should be sent to ensure timely reporting, with additional information provided as soon as it is known. Additional information received for an event (follow-up or corrections to the original event data) needs to be detailed on a new **Serious Adverse Event Reporting Form**.

SAEs that are deemed to have a causality of **"not related"** to the IMP (i.e. are not SARs), **do not** need an expectedness assessment against the RSI to assess whether they meet the criteria for a SUSAR.

Local research governance procedures at each site (e.g. NHS Trust), should also be followed.

5.4 SAFETY OVERSIGHT AND GOVERNANCE

The Sponsor must ensure that appropriate governance structures are in place to oversee participant safety throughout the trial.

Depending on the design and risk level of the trial, this may include:

- a Trial Management Group (TMG)
- a Trial Steering Committee (TSC)
- an Independent Data Monitoring Committee (IDMC) or Data and Safety Monitoring Board (DSMB).

These bodies may review aggregated safety data and provide recommendations to the Sponsor regarding:

- continuation of the trial
- protocol modifications
- implementation of additional risk mitigation measures
- termination of the trial where safety concerns arise.

The structure and responsibilities of these committees must be described in the trial protocol.

6. FOLLOW-UP OF ADVERSE EVENTS

All adverse events must be followed up until symptoms cease or the condition becomes stable. The **Adverse Event Record Sheet** requires a judgement on outcome, rating the adverse event as resolved (1), resolved with sequelae (2), persisting (3), worsened (4), fatal (5), or not assessable (6).

6.1 CONTACT DETAILS FOR ADVERSE EVENT REPORTING

Participants should be advised to contact the PI to report any unexpected occurrence or effect which they think might be related to the study medication. In addition to the participants themselves, pharmacy staff and other healthcare professionals responsible for the clinical care of the participant may notice suspected adverse events/reactions. It is essential that contact details for the study team are provided to anyone who may be in a position to recognise any change in the participant's behaviour or functioning, abnormal test results or untoward medical occurrences that may be related to the study medication. The most appropriate local contact details for a member of the study team must be included on the ethically approved **GP Letter**. The CI should include all SAR's and SUSAR's in the annual safety report (section 3.5).

7. SUSARS

Any SUSARs that occur during a clinical trial in the UK must be reported to the licensing authority under regulations 33 and 34 of the Clinical Trials Regulations, including those that:

- are associated with comparators and placebos (where an SAE is related to placebo)
- occur at non-UK sites if there are also trial locations in the UK
- occurred during the trial but were identified after trial completion

Any AE that the PI evaluates as serious, is suspected of having a causal relationship to the trial medication, trial comparator or placebo (as applicable) and is unexpected, will require **expedited** reporting to the RGIT, MHRA and to other organisations as required under the terms of the individual contracts (e.g. relevant pharmaceutical companies, NHS Trusts). Systematic failure to report SUSARs for a trial or a product(s) to the licensing authority in line with applicable regulatory requirements and guidance may be considered a serious breach.

If the CI, or Trial Management Group if appropriate, is not in agreement with the "expectedness" decision of the PI, the CI cannot overrule the PI's decision. Both opinions should be recorded on the SAE form.

SUSARs should be reported following the timelines in this SOP 0via the e-SUSAR electronic reporting system.0

The minimum data required for reporting SUSARs to the MHRA are:

- valid EudraCT and/or IRAS number (where applicable)
- sponsor study number
- one identifiable coded participant
- one identifiable reporter
- one SUSAR
- one suspect IMP (including active substance name code)
- a causality assessment

In addition, in order to properly process the report electronically, the following administrative information should be provided:

- the sender's (case) safety report unique identifier
- the receipt date of the initial information from the primary source

- the receipt date of the most recent information
- the worldwide unique case identification number
- the sender identifier

Following submission of a SUSAR, the sponsor should expect to receive acknowledgement of the submission within 48 hours. If an acknowledgement is not received then the sponsor should contact the E2B support team (E2B.support@mhra.gov.uk) to determine next steps, including whether resubmission is required.

There are certain scenarios where an exception to the usual SUSAR reporting requirements can be included in a protocol. All such exemption proposals must be clearly detailed in the protocol and can only be put in place following approval by the licensing authority and ethics committee. Failure to seek such approvals prior to implementing any exceptions may result in a serious breach.

1) Exemption can be proposed for reports of deaths or SAEs also considered primary efficacy endpoints in trials with high mortality or high morbidity, where these efficacy end-points could also be SUSARs (and the integrity of the clinical trial may be compromised if the blind is systematically broken), and where such SAEs are therefore accepted to be 'expected' in the approved protocol. Under these circumstances the sponsor should clearly list which serious events would be treated as disease related and not subject to systematic unblinding and expedited reporting. For such trials, sponsors are strongly encouraged to appoint an independent DSMB in order to review safety data on the ongoing trial on a regular basis and, when necessary, to recommend to the sponsor whether to continue, modify or terminate the trial. The composition and operation of the DSMB should be described in the protocol. A specific adjudication committee or other safety review committee should also be considered, which includes members with specific expertise relevant to the endpoints. The DSMB/committee should regularly review emerging safety data, with a specific focus on any SAEs or SARs that are part of the primary endpoint. If a safety signal is identified, then further review is recommended and any appropriate actions should be taken. This may include unblinding of events and making a determination on whether any events should be reported as SUSARs (Please see the following link for an example: Clinical trials for medicines: collection, verification, & reporting of safety events - GOV.UK)

2) Exemption can be proposed for reports of deaths or SAEs considered as disease related events in the authorised protocol. However, careful assessment should be performed in cases where disease-related events appear to be enhanced by the IMP. A causality assessment is required for each SAE, and if the investigator considers a disease-related event to also be IMP- related and the event is both serious and unexpected then it must be reported as a SUSAR (Please see the following link for an example: Clinical trials for medicines: collection, verification, & reporting of safety events - GOV.UK)

7.1 TIMEFRAMES FOR EXPEDITED REPORTING

Fatal/life threatening SUSARs

The CI must inform the RGIT, MHRA and relevant pharmaceutical companies (if required under the terms of the contract) of fatal or life threatening SUSARs as soon as possible, but no later than **7 calendar days** after the CI has first knowledge of the minimum criteria for expedited reporting. For fatal and life-threatening SUSARs, the sponsor should report at least the minimum information as soon as possible (please see above) and in any case no later than seven days after being made aware of the case. In each case, relevant follow-up information should be sought and a report completed as soon as possible. This should be sent within an **additional 8 calendar days.**

Non- fatal and non-life threatening SUSARs
The CI must report all other SUSARs and safety issues to the RGIT, MHRA and relevant pharmaceutical companies (if required under the terms of the contract) as soon as possible, but no later than **15 calendar days** after the CI has first knowledge of the minimum criteria for expedited reporting. Further relevant information should be given as soon as possible.

There may be cases where a SUSAR turns out to be fatal or life-threatening, when initially it was considered as non-fatal or not life-threatening. The non-fatal or non-life-threatening SUSAR should be reported as soon as possible, but within 15 calendar days. The updated fatal or life-threatening SUSAR follow-up report should then be made as soon as possible, but within a maximum of 7 days after first knowledge of the reaction being fatal or life-threatening. In cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening and the initial report has not yet been submitted, a combined report should be created and submitted via ICSR.

It may transpire, after the initial reporting, that the event is not a SUSAR, for example due to lack of information on causality, seriousness, or expectedness (hereinafter referred to as ‘downgrade’). Downgrades should be considered as relevant information. Examples of non-relevant information are minor changes of dates or corrections of typographical errors in the previous case version”. In situations where a SUSAR report has been submitted to the ICSR but the event is later downgraded, the team should update the Safety Report for the event to clearly show this downgrade and re-submit this via ICSR with a cover letter which quotes the original case number and clarifies the decisions/reasoning behind the downgrading of the event.

7.2 URGENT SAFETY MEASURES

The Chief and Principal Investigators have the authority to deviate from the protocol if doing so relates to the immediate safety of a participant, where continuing to follow protocol would put that participant at risk. This is classed as an urgent safety measure and must be reported to the RGIT, MHRA and REC within **7 calendar days** of the occurrence (but ideally within 24-hours). This may be reported verbally in the first instance but must be supported by a written report as soon as information is available. For more information, please refer to RGIT_SOP_037 Deviations, Violations and USMs.

7.3 REPORTING SUSARS TO THE MHRA

The e-SUSAR system has now been replaced with the Individual Case Safety Report (ICSR) Portal and is used to submit single reports: ISCR Submissions

When a new study begins, a member of the study team will be nominated to be responsible for entering the data onto the Portal and an account will be created for them on the ISCR Portal by RGIT CTIMP Team. In the event that a SUSAR occurs during the trial, the team member will need to create and submit a report via the ICSR Portal within the defined timeframes for safety reporting of a SUSAR.

The RGIT will require the contact details of the person(s) responsible for entering the data onto the ISCR Portal so that user accounts can be generated. Each user will only be given permission to access those trials they have responsibility for.

The MHRA gateway (cited on 19 Jan 2024) s used to submit bulk reports. To gain access to the MHRA Gateway you need to register to another portal called MHRA Submissions.

There are two user reference guides which contain step by step guidance on the processes:

- Registration for ICSR Submissions (cited on 19 Jan 2024)
- Registration for MHRA Gateway (cited on 19 Jan 2024)

For trials where the AHSC is acting as Legal Representative for a non-EU organisation, the sponsor has the option to register their organisation as an administrator for the ISCR system or access the system via the AHSC account if the data are being entered by an AHSC staff member.

For trials ongoing in both the UK and in European member states, dual reporting is needed. You will need to report each SUSAR to both the MHRA and to the European Medicines Agency's (EMA's) Eudravigilance Clinical Trial Module (EVCTM).

For more information, please visit the
Clinical trials for medicines: manage your authorisation, report safety issues - GOV.UK (www.gov.uk) (cited 19 Jan 2024)

7.4 Unblinding

For blinded trials involving a placebo and an active drug, seriousness, causality and expectedness should be evaluated as though the patient was on active drug.

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial and those responsible for data analysis and interpretation of results at the conclusion of the study. It is important that the details of the unblinding process are included in the trial protocol. As a general rule, only SUSARs on which the treatment allocation of the participant is unblinded should be reported by the sponsor to the licensing authority.

The investigator should only unblind the treatment allocation in the course of a clinical trial if this is relevant to the safety of the participant (i.e. in an emergency). A separate procedure should exist for SARs unblinded for emergency purposes for the clinical management of SARs by the investigator. Failure to have in place a suitable unblinding procedure may result in a serious breach in the event a participant requires emergency treatment where the attending physician is not able to unblind their treatment allocation.

With regards to the sponsor, when an event may be a SUSAR, the blind should be broken by the sponsor only for that specific participant. The sponsor must unblind the treatment for safety evaluation and regulatory reporting purposes if an SAR is unexpected as per the RSI of the IMP. The unblinding is not necessary for SARs assessed as expected for all IMPs for the purposes of expedited reporting as these would not meet the definition of a SUSAR.

Please see the "Unblinding Algorithm" via the following link: PowerPoint Presentation

Combination products, that is, either a fixed dose combination (FDC) or 2 separate IMPs given simultaneously, should have a clearly defined process in the protocol for unblinding in the event of an SAR.

A FDC product is generally expected to have a single RSI and therefore any SAR should have expectedness evaluated against events listed in that RSI.

For a combination where 2 separate IMPs are given simultaneously it is usual for each IMP to have its own IB (or SmPC) and therefore the combination arm will have 2 RSIs. Any SAR should be evaluated with consideration for both RSIs. If the event is unexpected for one or both IMPs in the combination, then the participant should be unblinded and a SUSAR reported appropriately.

An IDMC has access to semi-blinded or unblinded data and can oversee the assessment of emerging risks, such as an increase in frequency or severity of adverse events. The committee's assessments are carried out without disclosure to the trial team. They may recommend protocol modifications, or termination of the study, if they detect serious safety issues. In addition, the chairman of an IDMC might be able to play a role in unblinding individual reports of SUSARs for expedited reporting (if this could be managed within the requisite timeframes) and SSARs for annual reports.

7.5 REPORTING TO PI'S INVOLVED IN STUDY

Investigators do not need to be informed of SUSARs, but the CI may wish to notify investigators of the occurrence through a "Dear Investigator" letter or an updated Investigator's Brochure (IB).

7.6 REPORTING GUIDELINES: NON-IMP STUDIES

If a research participant experiences an SAE, you should report this to the relevant Research Ethics Committee and the Research Governance and Integrity Team, Imperial College AHSC, wherein the opinion of the Chief Investigator the event was:

- '**related**': resulted from administration of any of the research procedures; **and**
- '**unexpected**': the event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the CI becoming aware of the event, using the HRA's Non-CTIMP safety report to REC form. The form should be completed in typescript and signed by the chief investigator.

For SAE reporting guidelines for ICREC/SETREC studies refer to RGIT_SOP_045_ICREC Safety Reporting (*cited on 04 Dec 2023*).
Reports of double-blind studies should be unblinded.

7.6.1 ANNUAL REPORTS

For CTIMPs, please refer to RGIT_SOP_035_Developmental Safety Update Reports. These now replace the previous Annual Safety Report system for MHRA regulated trials.

7.6.2 ADVERSE EVENT REPORTING FOR INTERNATIONAL TRIALS

Clinical trials that involve sites outside of the UK must also follow the requirements of the countries in which the trial is taking place.

The procedures for reporting relevant events onwards to regulatory and ethics committees should be included in any agreements between international groups performing the trial. The protocol and/or study specific SOP should specify procedures for both the timing and format of reports of SUSARs in sites outside the EU.

7.6.3 REPORTING SUSARS TO THE ETHICS COMMITTEE

The reporting requirements of the main ethics committee responsible for the trial in each country should be established prior to the start of the study. These requirements will vary and therefore it should be detailed in the protocol/study specific SOP which SUSARs will need to be reported and where they should be sent. In the UK, RECs no longer evaluate UK SUSARs

7.6.4 REPORTING SUSARS TO THE COMPETENT AUTHORITIES

For trials taking place within the EU, the CI must ensure that **all** SUSARs are reported to the competent authority for each country in which the trial is taking place. Reporting will be via EudraVigilance.

For trials where Imperial College AHSC is Sponsor, but where all sites are outside the EU, there is no requirement to report SUSARs to the MHRA. The reporting requirements of the authorities in the participating countries must be complied with.

7.6.5 ANNUAL SAFETY REPORT/DEVELOPMENTAL SAFETY UPDATE REPORT FOR INTERNATIONAL TRIALS

An annual safety report should be submitted to the main REC and competent authority in each EU country that has a site participating in the trial (see section 3.5). This should include **all** SSARs and SUSARs occurring in **all** countries participating in the trial.

The requirements for countries outside the EU should be included in the protocol/study specific SOP. Annual reporting should take place as required.

7.6.6 SAFETY SIGNAL DETECTION AND EVALUATION

The Sponsor and CI, in conjunction with the pharmaceutical company providing the IMP for the study, must ensure that safety data are reviewed periodically to detect any emerging safety signals that may affect participant safety or the benefit-risk balance of the trial. This is normally done post-marketing of the drug thus the company may request information to complete their dossier and submit their periodic safety update report (DSUR).

Safety signal detection may include:

- periodic review of cumulative adverse event data
- analysis of trends in frequency or severity of adverse events
- review of external safety information relating to the investigational medicinal product
- review of safety data from other ongoing trials.

Where significant safety concerns are identified, the Sponsor must determine whether further actions are required. These actions may include:

- modification of the protocol
- implementation of urgent safety measures
- notification to regulatory authorities and ethics committees
- suspension or termination of the trial.

Independent oversight bodies such as Independent Data Monitoring Committees (IDMCs)/ Data and Safety Monitoring Board (DSMBs) may review emerging safety signals and provide recommendations to the Sponsor.

8. REFERENCES

Medicines: clinical trials hub - GOV.UK

Data Protection Act (2018)
Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (cited 03 Dec 2023)

Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)
EudraVigilance Support Guide (cited on 03 Dec 2023)

The Medicines for Human Use (Clinical Trials) Regulations 2004 Part 5
(cited on 03 Dec 2023)

National Research Ethics Service guidance on safety reporting (cited on 19 Jan 2024)

MRC/DH joint project, Workstream 6: Pharmacovigilance (cited on 19 Jan 2024)

Clinical trials for medicines: manage your authorisation, report safety issues - GOV.UK (www.gov.uk) (cited 19 Jan 2024)

9. APPENDICES

The following Appendices list the following Templates associated to this SOP which can be found on the SOP, Associated Documents & Templates page.

Appendix 1: Sample SAE Form – RGIT_TEMP_003
Appendix 2: Flowchart for Reporting and Assessing Adverse Events in CTIMPs sponsored by Imperial College - RGIT_TEMP_004
Appendix 3: MHRA Addresses

Developmental Safety Update Reports should be provided to the MHRA using the MHRA Portal (cited on 14Dec2020)
The same guidance for submitting clinical trials applications via MHRA Portal applies, but please select regulatory activity G0042 - Development Safety Update Reports.

eSubmission Guidance**:** Guidance has been published on the structure and format of electronic submissions for both human & veterinary medicinal product submissions. (cited on 03 Dec 2023)

Guidance - Register to make submission to MHRA

Guidance on submitting clinical trial safety reports