SOP number	**55.001**	Version	**8.0**
Title	**Pharmacovigilance in Clinical Trials of Investigational Medicinal Products (Glasgow Clinical Trials Unit)**		

Prepared by Signature	Marc Jones Date
Approved by Signature	Caroline Watson Date
Released by Signature	Julie Brittenden Date

SOP category	NHS GG&C Sponsor Pharmacovigilance
Staff category	

Staff Category	R	A	C	I
R&I Pharmacovigilance	X			
R&I Research Governance Manager		X		
Sponsor Research Co-Ordinators			X	
Project Managers			X	
R&I Pharmacy			X	
R&I Monitoring			X	
Chief Investigator				X
Principal Investigator				X

1. Scope

This procedure applies to NHS GG&C staff with Sponsor responsibilities. CIs will be provided with a copy (marked as an uncontrolled copy) of this SOP for their information.

2. Purpose

Pharmacovigilance is defined by the World Health Organisation (WHO) as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long-term and short-term side effects, of medicines.

The Medicines for Human Use (Clinical Trials) Regulations 2004 transposed EU Directive 2001/20/EC into UK law and set out specific requirements for pharmacovigilance in clinical trials of investigational medicinal products (CTIMPs).

The purpose of this SOP is to describe the responsibilities for pharmacovigilance in CTIMPs sponsored by NHS Greater Glasgow and Clyde (NHS GGC) or co-sponsored with the University of Glasgow.

The delivery of these responsibilities will be facilitated and supported by the NHS GG&C Pharmacovigilance Office and the Cancer Research UK Clinical Trials Unit (CRUK-CTU) Pharmacovigilance Office in liaison with other functional departments within the GCTU and CRUK-CTU, such as the Robertson Centre for Biostatistics (RCB) for reporting, Glasgow Clinical Research Facility for training and NHS GGC Research and Innovation.

This SOP describes the procedures for (co-)sponsored CTIMPs supported by the NHS GG&C PV Office. Procedures for (co-)sponsored CTIMPS managed by the CRUK CTU PV Office are described in CRUK CTU SOPs.

Definition of Sponsor for Pharmacovigilance
When sponsorship responsibilities are allocated under the Clinical Trials Regulations, one organisation or individual will be named as the Sponsor for Pharmacovigilance. For trials co-sponsored between NHS Greater Glasgow and Clyde (NHS GG&C) and the University of Glasgow, NHS GG&C is responsible for Pharmacovigilance. The Sponsor may then delegate the tasks and functions as necessary to comply with the Regulations - for example, to the CI or other investigators.

Sponsor Responsibilities for Pharmacovigilance
The Sponsor is responsible for providing training to the CI, local Principal Investigators (PIs) and trial teams in the processes required.

The Sponsor of a CTIMP is responsible for promptly notifying:

- Investigators
- Research Ethics Committee (REC)
- Competent Authorities (MHRA in UK)
- IMP (Investigational Medicinal Product) manufacturers

Of findings that could:

- Adversely affect health of participants
- Impact on conduct of trial
- Affect the authorisation and continuation of the trial

Further Responsibilities:

- Ensure an appropriate Reference Safety Information (RSI) is prepared and regulatory approval is obtained for each IMP used within a trial and that this is reviewed at least annually, in addition to the monthly checks carried out by pharmacy for the purposes of clinical management.
- Where appropriate; keep records of all Adverse Events (AEs) reported by investigators
- Recording and reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) to appropriate authorities within specified timelines
- Ensure investigators are informed of SUSARs
- Ensure all SUSARs, including those in third countries, are entered into the European safety database (EudraVigilance) where applicable.
- Provide annual list of SUSARs and submit a safety report to the appropriate authorities

Investigator Responsibilities
The CI has overall responsibility for the conduct of the CTIMP.

The PI, who may also be the CI in a single-site trial, has responsibility for the conduct of the CTIMP at the host site.

In CTIMPs sponsored by NHS GG&C, or co-sponsored with the University of Glasgow (UofG), the delivery of Pharmacovigilance activity within the trial is delegated to the CI. However, the ultimate responsibility and accountability for Pharmacovigilance remains with NHS GG&C.

It is essential that the responsibilities for Pharmacovigilance activities within the trial are documented and agreed by all parties.

3. Procedures

3.1. Prior to Study Start:

The proposed safety recording, notification and reporting procedures will be detailed in the trial protocol and will be reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) during the Clinical Trials Authorisation (CTA) process with oversight by the REC.

The PV Office will maintain a log of trials requiring SAE processing saved within the filestore. PV Office personnel must be formally notified of such trials in advance by the PV and Safety Manager and this notification will include the provision of the Sponsor Safety Reporting Plan (Form 55.001A).

Risk Assessment
During the initial stages of the trial, the PV and Safety Manager will participate in the risk assessment of all trials (co-)sponsored by NHS GG&C/UofG, SOP 51.004. The level of safety reporting will be linked to the phase of trial and the level of risk for the participant above standard care in the condition being studied.

In general, the higher the level of risk, the higher the level of safety reporting required, however this should always be discussed with the CI. The levels of risk are defined as per the MHRA Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products (2011).

These levels are defined as follows:

- Type A = No higher than the risk of standard medical care
- Type B = Somewhat higher than the risk of standard medical care
- Type C = Markedly higher than the risk of standard medical care

The appropriate selection is made during the Risk Assessment process and recorded on Form 51.004A.

Based on these criteria, the level of reporting required for level of risk can be defined as per the table below. Where "Full" is stated, this implies that all AEs, ARs and SAEs are collected unless there is a strong clinical basis for an exclusion.

Risk

Risk	Phase of trial	AE reporting	AR reporting	SAE reporting
C	I	Full	Full	Full
C	IIa	Full	Full	Full
C/B	IIb	Full*	Full	Full*
B	III high/medium risk	Reduced*	Full*	Full*
B/A	III low/medium risk	Medical records	ARs of special interest	Reduced e.g. exclude most common disease related events or ARs only
A	IV	Medical records	Medical records	ARs only

Safety reporting

*Exclusions can be made, for example disease-related processes, etc. Any exclusion must be justified within the protocol.

In addition, the Phase/Risk of a trial will impact on the level of SAE review in a trial. PI and CI review are required for all trials - however, the timeline for clinical review by the CI may differ and will be documented in the individual trial protocol but must allow time for review within the regulatory timeframes for the submission of a SUSAR; that is, 7 calendar days for life threatening or fatal events, and 15 calendar days for all other events.

The table above is provided for general guidance only and any safety reporting should be discussed amongst the trial management team prior to submission to the MHRA. The process will be detailed within the protocol.

The data collected within the SAE form may differ between trials on a risk dependent basis will be defined by the Sponsor for each trial on an individual basis.

A generic form can be found on the GCTU website, and this can be used in circumstances requiring paper reporting. This form can be found here:

https://www.glasgowctu.org/Home/00-safety-reporting/

The trial risk assessment will be revisited if there are any changes to the process and following substantial amendments as per SOP 51.004: Risk Assessment.

Adverse Event Recording & Reporting

The protocol will document:

- How AEs will be identified (e.g. by enquiry at study visits, from lab reports, etc.)
- How AEs will be recorded in the eCRF or paper CRF and patient records
- How AEs will be assessed for seriousness, causality, expectedness and severity, including whether the responsibility for the initial review lies with the PI, CI or both
- Any events classed as serious which should be excluded from reporting to the Sponsor (if an incident is anticipated or likely as a result of the study population or condition, it can be excluded from the SAE reporting process **only** if it is clearly identified as a likely outcome in the study protocol).
- The period of time during which investigators should notify the Sponsor of SAEs. This period of time will be dependent on the risks associated with the trial. The standard period of time is from randomisation until 30 days following the last administration of trial drug but this should be defined on a per trial basis. However, should an event occur following this protocol defined time period that meets the regulatory definition of serious and is considered related to the trial treatment, this remains reportable as an SAE indefinitely. In trials where trial-specific procedures occur following the consent process but prior to randomisation, safety data will be collected from the date of consent until the end of the protocol defined time period.
- The information source used to inform the RSI for the trial, this may be section 4.8 of the SmPC or a specifically titled section of the IB.
- Details of pharmacovigilance unblinding procedure, if appropriate
- The requirements for the expedited reporting of any SAE assessed as a SUSAR and arrangements for informing investigators
- Development Safety Update Report (DSUR) preparation and reporting

Any delegation of pharmacovigilance activities by the Principal Investigator (e.g. AE recording, assessment or reporting) must be documented on a Delegation Log in the Investigator Site File.

AEs will be collected within the eCRF or by using paper CRFs as detailed within the protocol and within the Safety Reporting Plan for the trial.

Collection of SAEs via eCRF

The Pharmacovigilance and Safety Manager will be involved in the specification of the format of SAE reports and associated data collection. The Pharmacovigilance and Safety Manager will liaise with the data management centre during the CRF design stage in order to implement an SAE form that collects the required level of information for a particular trial.

3.2. During a Trial (See Flow Chart, Appendix 2)

3.2.1. Adverse Events (AEs)

AEs will be recorded, notified, assessed, reported, analysed and managed in accordance with the Clinical Trials Regulations and the approved study protocol.

At each study visit, any AE reported to trial site staff must be recorded in participant medical records. AEs will be captured within the eCRF/CRF as required by the protocol.

AEs must be assessed for seriousness and causality. SAEs must also be assessed for expectedness and severity.

The clinical review and assessment of AEs must be undertaken by the CI or PI, or another appropriately-qualified clinician who has been delegated this task, as documented on the Delegation Log.

The assessment may also be undertaken by another party (e.g. Data Monitoring Committee (DMC) or Trial Steering Group (TSG)). This should be detailed in the protocol.

In randomised, double-blind, placebo controlled studies, AEs should be assessed as though the patient is taking the study drug.

All SAEs must be reported to the Sponsor's PV Office immediately (within 24 hours) of the event being reported to the study team.

3.2.1.1. Assessment of Seriousness

This assessment is based on the regulatory definitions of seriousness. These definitions should be included in the trial protocol.

An AE is serious if it:

a) Results in death
b) Is life-threatening[1]
c) Requires hospitalisation[2] or prolongation of existing hospitalisation
d) Results in persistent or significant disability/incapacity
e) Consists of a congenital anomaly/birth defect
f) Jeopardised the patient or required intervention to prevent one of the above[3]
g) Other medically significant event[3]

f) and g) are both commonly used, and while the definition differs slightly are interchangeable.

Note:
[1]Life-threatening in the definition of an SAE or Serious Adverse Reaction (SAR) refers to an event in which the participant 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.
[2]Hospitalisation is defined as an inpatient admission. Pre-planned hospitalisations (e.g. for pre-existing conditions which have not worsened or for elective procedures) do not constitute an SAE.
[3]Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AEs/ARs that are not immediately life-threatening or do not result in death or hospitalisation but jeopardise the participant or require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. In addtion events that do not meet the seriousness critieria that are unexpected may be reported where option g is a criterion.

The term "severe" is often used to describe the intensity (clinical severity) of a specific event. This is not the same as "serious," which is a regulatory definition based on patient/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

Confirmation of seriousness by the local investigator
The local investigator will be asked to confirm the seriousness of an event at the time of PI review; including determining if the event is reportable. Where CI is required they will also be asked to confirm the seriousness of an event at the time of their review including determining if the event is reportable.

3.2.1.2. Assessment of Severity

The intensity of the event should be assessed by the reporter and described using the following categories:

Mild: Awareness of event but easily tolerated
Moderate: Discomfort enough to cause some interference with usual activity
Severe: Inability to carry out usual activity

In some specialities other scales may be used for assessing severity, for example in oncology trials the Common Terminology Criteria for Adverse Events (CTCAE) is more commonly used. This is acceptable and will be detailed within the trial protocol.

Confirmation of Severity by local investigators
Local investigators will be asked to confirm the severity of an event at the time of PI review.

3.2.1.3. Assessment of Causality by local clinical investigators

Does the AE have a "reasonable causal relationship" with trial medication? The following categories are recommended, but this is not mandatory and other more granular categorisations are acceptable:

Unrelated: The SAE is not considered to be related to the study drug

Related: The temporal relationship, known effects of a drug, its therapeutic class, challenge testing, and an absence of a more likely explanation, suggest that the event is related to the study drug

A related AE is an **Adverse Reaction (AR).**

A related SAE is a **Serious Adverse Reaction (SAR).**

Causality should be assessed by the PI or an authorised co-investigator at each individual site within 7 calendar days of submission to the Sponsor for fatal or life-threatening SAEs, or within 15 calendar days of submission for all other SAE outcomes.

The CI or their clinical delegate may provide an assessment of causality provided by the investigator submitting the event. If the CI does not believe the event to be caused by the trial drug, this is relayed to the PI.

The Sponsor, or the CI acting on behalf of the Sponsor cannot downgrade assessments of causality provided by the local authorised clinicians at site. The CI (or their delegate) or Sponsor may discuss the event with the authorised clinician either directly or through the PV Office and where no

agreement is reached the event is reported as per the local clinical investigators' assessment of causality.
Where the opinion of a PI and the CI (and therefore Sponsor) differ, this must be clearly marked in the reports submitted to the MHRA and REC.

For SAEs thought to be unrelated, the investigator should use clinical judgement and knowledge of the patients' medical history, ongoing disease processes, trial procedures, concomitant medications, and other circumstances to identify potential causative factors other than the IMP.

In the event the local investigator does not carry out an assessment of causality within the seriousness dependent regulatory timeframe and the event is within the protocol defined time period for expedited reporting of SAEs the Sponsor must assume the event is related and expectedness must be assigned as per section 3.2.1.4.

3.2.1.4. Assessment of Expectedness

Where an event is considered to be related to the study medication, the CI (or their delegate) on behalf of the Sponsor or the Sponsor PV and Safety Manager (or their delegate) should carry out an assessment of the expectedness of the reaction (i.e. is the reaction a recognised adverse effect of the medication or is it unexpected?).

The expectedness of an adverse reaction must be assessed against the RSI (the list of expected reactions detailed in a section of the IB or SmPC for the IMP) approved by the MHRA at the time of onset of the event.

Assessment of expectedness will be carried out by the CI (or their delegate) or by the Sponsor PV and Safety Manager (or their delegate). Responsibility for the assessment of expectedness should be detailed in the trial protocol during development and confirmed during risk assessment.

Expectedness is assigned as per the following definitions:

Expected: Consistent with the toxicity of the IMP listed in the approved RSI in place at the time of the event.

Unexpected: Not consistent with the toxicity of the IMP listed in the approved RSI in place at the time of the event.

Any AE that is assessed as **serious**, is suspected of being **related** to the trial medication and is **unexpected** as per the relevant approved RSI is a **SUSAR** and requires expedited reporting to the MHRA/Ethics Committee. See Section 3.6.

3.3. Non-Investigational Medicinal Products (NIMPs)

Medicines that are not the object of investigation (i.e. other than the tested product, placebo or active comparator) may be supplied to participants in a trial and used in accordance with the protocol. This might be, for example, medicinal products such as support or rescue/escape medication for preventative, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the participant. These medicinal products are called Non-Investigational Medicinal Products (NIMPs). NIMPs do not fall within the regulatory definition of IMPs.

Additional details of the types of products which are defined as NIMPS can be found in: Guidance on Investigational Medicinal Products (IMPs) and 'Non Investigational Medicinal Products' (NIMPs) (Rev. 1, March 2011) found https://health.ec.europa.eu/system/files/2016-11/imp_03-2011_0.pdf

However, if NIMPS are used in a trial, the investigator must assess whether an AE could be related to the NIMP or to an interaction between the IMP and the NIMP.

A serious, untoward and unintended response to a NIMP is not a SUSAR and therefore does not require expedited reporting.

A serious, untoward and unintended response which results from a possible interaction between a NIMP and an IMP is a SUSAR and will require expedited reporting.

3.4. Reporting Requirements

3.4.1. Notifying the Sponsor

All SAEs must be reported to the Sponsor PV Office immediately (within 24 hours) using a Sponsor-approved SAE report form generally via the trial eCRF.

The SAE report form used within the trial is dependent on the level of risk as defined in Section 3.1 and will be provided to all sites at the time the trial opens to recruitment.

Paper SAE Reporting

This is completed by appropriate site staff delegated to do so on the site Delegation Log as follows:

1. The generic SAE form is downloaded from the Glasgow CTU website (https://www.glasgowctu.org/), printed, completed by an authorised member of staff and signed. The form is then emailed (pharmacovig@glasgowctu.org) to the PV Office and a copy is placed in the Investigator Site File.
2. If necessary a verbal report can be provided by contacting a member of the trial management team. This must be followed up within 24 hours by a signed written (or electronic) report.

Electronic SAE Reporting

Following appropriate training and issuance of login details, the approved SAE form can be completed electronically via the study web portal. If the event is classed as a SUSAR, additional information will automatically be required to comply with regulatory requirements. Once completed electronically, a copy of the report will be printed off and stored in the relevant section of the Investigator Site File.

Should the required information be unavailable at the time of initial reporting, the PI/CI (or designee) must ensure that the missing information is forwarded to the PV Office as soon as it becomes available. The report should indicate that this information is follow-up information for a previously-reported event. The follow-up information can be sent electronically or on paper as above.

Initial and follow-up reports should clearly identify participants by unique code numbers assigned to the trial participants at registration/randomisation.

In blinded trials, SAE and SAR reporting should maintain the blind unless it is considered necessary to break the blind in the interest of patient safety (see Section 3.8).

3.5. Processing of Serious Adverse Events by the PV Office

3.5.1. Receipt and Review of an Initial SAE

Following receipt of an initial SAE by the PV Office, the forms should be reviewed for completeness and consistency within 2 working days. The detail regarding processing of SAEs is documented within Guideline 55.001G - PV Office Processing for Clinical Trials of Investigational Medicinal Products. Day zero is defined as the day the SAE is reported to the Sponsor by the site and is the day the timelines for the Pharmacovigilance processes start.

Where items are missing or inconsistent, a data query must be raised with the site personnel responsible for submitting the SAE in a timely manner.

In addition, for those SAEs received via paper CRF and receipt of the SAE acknowledged as soon as possible. The reporter should be reminded of the need to report the event via the eCRF when able

The date an SAE is by any means received is defined as day zero.

3.5.2. PV Office Timelines for Clinical Review of SAEs

The regulatory timelines for SUSAR reporting are: 7 calendar days for fatal or life-threatening SAEs or 15 calendar days for all other SAE outcomes. To enable the PV Office to adhere to the regulatory requirements, this 7/15 calendar day timeframe is directly translated into the maximum timeframe for review and sign-off of SAEs.

SAEs should be assessed for causality by the PI within a timeframe allowing for sufficient time for Sponsor review of expectedness, discussions required to take place regarding the causality and expectedness of the event, and submission to the MHRA and REC if required.

3.5.3. Follow-up SAEs Review

Follow ups and completion

Serious adverse events; wherever possible, should be followed up to completion before database lock. On occasion it may not be possible for all events to be followed to completion and in such circumstances this should be documented.

Note: completion is defined by the resolution of events (including with sequelae), death, a condition being present at the time of death, or with a criteria of unknown if no further information can be obtained.

Review of Follow Ups by Local Investigators

Follow-up SAEs are subject to an updated assessment of causality by the local clinical investigator should the following criteria be met:

a) Initial review by the local clinical investigator identified that the event is unrelated to IMP and a follow up indicates that the event is related to IMP or vice versa.
b) New events have been added to the narrative that may require submission of subsequent events, or the event term has changed significantly

Review of Follow Ups by the Chief Investigator and/or Sponsor
Follow-up SAEs are subject to an updated assessment of expectedness by the local clinical investigator should the following criteria be met:

a) Following an initial assessment of expectedness of a SAR the seriousness of the event has changed for the worse
b) Following an initial assessment of expectedness of a SAR the outcome of the event has changed for the worse
c) Initial review by the local clinical investigator identified that the event is unrelated to IMP and a follow up indicates that the event is related to IMP
d) New events have been added to the narrative that may indicate a requirement for further reporting or the event term has changed significantly

In both scenarios the SAE should be processed as per section 3.5.1 and within the timelines set out in section 3.5.2.

3.5.4. CI Review of SAEs and SUSARs

For phase 1 and 2a trials all SAEs should be reviewed by the CI or their delegate within the timelines detailed in section 3.5.2. There may be a requirement for further review of causality and expectedness by the CI on a trial by trial basis. This will be discussed during the risk assessment and study initiation meetings and documented within the pharmacovigilance plan.

In all other trials, the CI must review all SARs within an agreed timeline and there may be a requirement for review of SAEs by the CI within an agreed timeframe. This will be discussed during the risk assessment and study initiation meetings and documented within the pharmacovigilance plan.

The CI or their delegate will review all SAEs that are related and unexpected.

3.6. Expedited Reporting of SUSARs to the MHRA/REC:

3.6.1. What Requires Reporting?

All SUSARs occurring within a trial taking place within the UK (including SUSARs originating outside the UK) must be reported to the MHRA.

Only SUSARs originating in the UK must be reported to the REC.

3.6.2. Reporting Process and Timelines

Processing of SUSARs is detailed within Guideline 55.001B - PV Office – Expediting SUSARs. Following receipt of a potential SUSAR, the PV Office administrators will notify the PV and Safety Manager and CI (including delegates and local investigator if required) of the event. The CI or Sponsor PV and Safety Manager or their delegates will assess and review the SAE report and confirm and document if an event fulfils SUSAR criteria.

Where an event is correctly reported as a SAR or SAE and later develops into a SUSAR, the timeline for reporting begins from the date when the Sponsor is aware of the change in status.

Where a SUSAR is confirmed in a blinded CTIMP, the treatment allocation for the participant will be unblinded by the Sponsor to facilitate appropriate reporting (See 3.8.2).
All SUSARs must be reported in an expedited fashion to the MHRA/REC.

The Clinical Trials Regulations set time limits for expedited reporting:

Fatal or life-threatening SUSARs: no later than 7 calendar days after the Sponsor has received the information containing the minimum reporting criteria and any follow-up information within a further 8 calendar days.

All other SUSARs: no later than 15 calendar days after the Sponsor has received the information containing the minimum reporting criteria.

The minimum criteria for reporting are:

- A suspected investigational medicinal product
- An identifiable participant (e.g. trial number)
- An adverse event assessed as serious and unexpected, for which there is a reasonable causal relationship
- An identifiable reporting source
- A EudraCT number or local study reference number (or, in the case of non-European community trials, the Sponsor's trial code number)

And, when available and applicable:

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

3.6.3. Reporting Responsibilities

Reporting to the MHRA, REC and other authorities, as required, will be undertaken by the PV Office in liaison with and on behalf of the CI as follows:

- MHRA – via the Individual Case Report (ICSR) system
- REC - a copy of the ICSR form with accompanying National Research Ethics Service covering sheet.

The PV Office, on behalf of the CI (or designee), is responsible for ensuring that all relevant follow-up information is requested for reporting to the MHRA/REC within the relevant time limits.

The ICSR system does not automatically update the European safety database (EudraVigilance). Where NHS GG&C/UofG are the Sponsor for trials taking place outside the UK the PV Office is responsible for ensuring that the local PV office is notified of a SUSAR requiring reporting in their country. The local PV office is responsible for reporting SUSARs to their local competent authority and if required into the EudraVigilance database to ensure that all relevant authorities are notified. The collaborating centres will also be responsible for reporting to their country's REC in line with local regulations.

For international trials, the Safety Reporting Plan will contain detailed guidance regarding the reporting requirements between the involved parties and/or countries.

Details on this process can be found in Guideline 55.001C.

3.6.4. Other Reporting Considerations for SUSARs

For events that have previously been reported to the MHRA via the ISCR system that have since been downgraded, the entry must be updated with a comment documenting the change in assessment stating that the event is now considered expected.

Where a site reports a fatal or life-threatening event classed as a SUSAR more than 24 hours after becoming aware of the event, the PV Office will make every attempt to meet the regulatory timeframe of 7 calendar days. The site must be reminded of the regulatory timelines.

3.7. Other Safety Issues requiring Expedited Reporting to the Sponsor

Events may occur during a clinical trial which do not fall within the definition of SUSAR and thus are not subject to the reporting requirements for SUSARs, even though they may be relevant in terms of participant safety.

Examples are:

- new events related to the conduct of a trial or the development of an IMP likely to affect the safety of participants, such as:
    - a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial
    - a significant hazard to the participant population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
    - a major safety finding from a newly completed animal study (such as carcinogenicity)
- a temporary halt of a trial for safety reasons if the trial is conducted with the same IMPs in another country by the same Sponsor, or via information obtained from another Sponsor utilising the same IMP in a clinical trial, recommendations of the Data and Safety Monitoring Board, if any, where relevant for the safety of participants,
- in the case of advanced therapy investigational medicinal products (ATIMPs), relevant safety information regarding the procurement or the donor.

These events/observations are not to be reported as SUSARs, but they might require other action, such as:

- urgent safety measures and their notification
- substantial amendments
- early termination of the trial

It is also recommended that the Sponsor informs the MHRA and the REC of any safety issues which might materially alter the current benefit-risk assessment of an IMP while not falling within the actions listed above.

3.8. Unblinding for Pharmacovigilance purposes

3.8.1. Emergency Unblinding

Emergency unblinding arrangements must be detailed in the protocol. Treatment allocation for participants within a clinical trial must only be unblinded if this is relevant to the safety of the participant.

3.8.2. Unblinding for SUSAR Reporting

Only SUSARs for which the treatment allocation of the participant is unblinded should be reported to the MHRA/REC. When an event may be a SUSAR the blind must be broken only for that specific participant. The blind should be maintained for persons responsible for the ongoing conduct of the

study (such as the management, monitors, investigators) and those responsible for data analysis and interpretation of results at the conclusion of the study.

Unblinded information must only be accessible to those who involved in safety reporting or persons performing ongoing safety evaluations during the trial. In general, unblinding for pharmacovigilance purposes will be carried out by the Pharmacovigilance and Safety Manager or PV Office, but may be delegated to other trained personnel if required.

Study-specific unblinding arrangements, including the requirement to unblind the treatment allocation when a potential SUSAR is identified, should be documented in the protocol or other study-specific document (e.g. Form 55.001A - Sponsor Safety Reporting Plan).

The CI (or designee) should review potential SUSARs in a blinded manner and must assume that the patient has received the trial study drug when assessing causality and expectedness.

For reporting purposes, only those SUSARs that are causally linked to the study drug will be reported to the MHRA and REC. However, onward reporting to investigators should take place in a blinded manner as per section 3.9.

Where the integrity of the clinical trial may be compromised if the blind is systematically broken (e.g. where efficacy endpoints in a trial could also be SUSARs) the Sponsor must specify in the protocol and reach agreement at the CTA stage, as to which serious events would be treated as disease–related and would therefore not be subject to systematic unblinding and expedited reporting.

3.9. Informing Investigators of SUSARs

Study PIs must be informed of SUSARs that have occurred in the trial. This is not required to occur within the 7/15 calendar day deadline, however it should occur in a timely, concise and practical manner to ensure that PIs remain fully-informed of all safety information.

In a single-centre UK study where the Sponsor has no other studies running with the same IMP, all other investigators at that site should be informed.

In multi-centre trials, all PIs within the trial must be informed.

The PV Office will forward a copy of any SUSAR report, with an accompanying cover letter, to the CI/Project Manager for onward distribution to co-investigators.

In blinded CTIMPs, SUSAR reporting to participating investigators will be blinded. The PV Office will forward a copy of a report of any event identified by the CI or Sponsor as a potential SUSAR (as a redacted copy of the SAE report from the study database) with an accompanying cover letter to the CI/Project Manager for onward distribution to co-investigators. No detail of the treatment allocation will be included in this report.

Any immediate safety concerns must be communicated to all concerned investigators in an expedited fashion.

3.10. Pregnancy

While not technically considered an AE or SAE, pregnancies occurring in CTIMPs require monitoring and follow-up.

The CI (or designee) must collect pregnancy information for female trial participants or female partners of trial participants. This includes participants 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).

Any pregnancy occurring in a female participant or female partner of a trial participant will be reported by the PI (or designee) to the PV Office (Sponsor) using the Pregnancy Reporting Form (available at https://www.glasgowctu.org/Home/00-safety-reporting/) within two weeks of the PI first becoming aware of the pregnancy. The participant will also be contacted to determine the outcome of the pregnancy and follow-up information forwarded to the PV Office. It may be necessary to monitor the development of the newborn for an appropriate period post-delivery. Any resulting SAEs should be reported as per the SAE reporting procedure above.

3.11. Development Safety Update Report (DSUR)

The Clinical Trials Regulations require that a DSUR is submitted to the MHRA and REC that approved the trial as soon as is practicable (but within 60 calendar days) of the anniversary of the issue of the CTA.

The DSUR will be prepared and submitted by the Sponsor Pharmacovigilance and Safety Manager in liaison with the CI. The content of this report and the procedure for preparation and submission are detailed in Guideline 55.002A PV Office – Creation and submission of Development Safety Update Reports and SOP 55.002 Preparation and submission of the Development Safety Update Report.

Note: There are separate non-statutory requirements for the submission of **annual progress reports** to RECs. These requirements are detailed on the NHS Health Research Authority website at: http://www.hra.nhs.uk/research-community/during-your-research-project/progress-reporting/

3.12. Unexpected Trends in SAE Reporting

No formal signal detection or trend analysis is currently performed by the Sponsor. However; for all CTIMPS trial data is reviewed by the independent data monitoring committee on at least an annual basis. Statistical monitoring may be used to identify significant differences between arms and where this is in place it will be recorded within the protocol and pharmacovigilance plan. Should an unexpected pattern of SAE reporting becomes apparent, the following procedure will be applied:

- Pharmacovigilance and Safety Manager alerted (if not already aware)
- CI alerted
- NHS GG&C R&I Research Governance Manager advised
- UofG Research Governance Officer advised if the trial is co-sponsored

3.13. Notifying NHS Trust/Health Board

Although not a requirement of the Clinical Trials Regulations, the PI at each centre participating in a trial should ensure that their organisation is notified, in accordance with the organisation's clinical incident reporting policy, of any relevant patient safety incidents that occur in the trial.

4. Referenced Documents

- SOP 55.002: Preparation and submission of the Development Safety Update Report (Glasgow Clinical Trials Unit)
- SOP 51.004:Risk Assessment
- Form 55.001A: Sponsor Safety Reporting Plan
- Guideline 55.001B: PV Office – Expediting SUSARs
- Guideline 55.001C PV Office – Submitting SUSAR reports to MHRA via ICSR
- Guideline 55.001G: PV Office Processing for Clinical Trials of Investigational Medicinal Products
- Guideline 55.002A: PV Office – Creation and submission of Development Safety Update Reports
- EU Clinical Trials Directive (2001/20/EC)
- The Medicines for Human Use (Clinical Trials) Regulations (UK SI 1031) as amended
- Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products (2011)
- Medicines and Healthcare products Regulatory Agency, Good Clinical Practice Guide, UK: TSO, 2012.
- NHS Health Research Authority (HRA) website: http://www.hra.nhs.uk/ (Accessed 03/02/2015)

5. Related documents

- The Importance of Pharmacovigilance: safety monitoring of medicinal products World Health Organization 2002 http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf
- Communication from the Commission — 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') (2011/C 172/01)
- Management of Safety Information from Clinical Trials: Report of CIOMS Working Group VI
- International Conference on Harmonisation (1996) Harmonised Tripartite Guideline for Good Clinical Practice
- The Scottish Executive Health Department Research Governance Framework for Health and Community Care (Second Edition, 2006)

6. Document history

Version	Date	Description
1.0	22/11/2007	Release of Version 1 (for review)
1.1	19/05/2008	Released to staff
2.0	18/06/2009	Revision of title for clarification. Revision of procedure for reporting to Sponsor.
2.1	12/10/2010	Addition of reference to Guideline 18.001 Revision of section 5.4 (Expedited reporting of SUSARs to the Research Ethics Committee (REC) and MHRA) Document template updated
3.0	15/02/2013	Revision of title Revision to incorporate SOP 18.002 Revision of Annual Safety Reporting requirements to incorporate requirements of DSUR

		Appendix 2 updated
4.0	Not released	New template Amendments to Staff category and Scope Clarification of requirement for unblinding for SUSAR reporting Incorporation of appropriate content from GCTU SOPs 18.007, 18.012, 18.014 Not released
4.1	15/12/2015	Update to Unblinding for SUSAR reporting section following advice from MHRA
5.0	15/07/2016	Reviewed and released as part of the SOPs reorganisation process. SOP category changed and SOP renumbered (previously 18.001). 'Prepared by' changed to Caroline Watson, 'Approved by' and 'Released by' changed to Julie Brittenden. References to other SOPs updated to reflect new structure. No changes to content.
6.0	20/12/2018	Reviewed and updated following appointment of Pharmacovigilance and Safety Manager Marc Jones. Addition of reference to Guideline 55.001G.
7.0	16/06/2020	Removes several sections no longer considered relevant. Includes Sponsor assessment of causality, and review of causality by local investigator only. Confirms the RSI that should be used to assign expectedness.
8.0	09/06/2023	Clarification of reporting outside the UK, and changes to several sections regarding review processes. Change of eSUSAR reporting to reflect replacement by ICSR submission system.

Appendix 1: Glossary

Adverse Event (AE)

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.

Comment: An adverse event 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, whether or not considered related to the investigational medicinal product

Adverse Reaction (AR)

Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

Comment: All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product 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.

Advanced Therapy Investigational Medicinal Product (ATIMP)

An advanced therapy medicinal product (ATIMP) is an investigational medicinal product which is either:

- a gene therapy medicinal product
- a somatic cell therapy medicinal product
- a tissue engineered product

Chief Investigator (CI)

In relation to a clinical trial conducted at a single trial site, the investigator for that site; or in relation to a clinical trial conducted at more than one trial site, the authorised health professional, whether or not they are an investigator at any particular site, who takes primary responsibility for the conduct of the trial.
Comment: This will be the clinician named on the Clinical Trial Authorisation (CTA) as having overall responsibility for the conduct of the study in the UK.

Clinical Trial

Any investigation in human participants, other than a non-interventional trial, intended -

a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products,
b) to identify any adverse reactions to one or more such products, or
c) to study absorption, distribution, metabolism and excretion of one or more such products.

Investigational Medicinal Product (IMP)

A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial -

a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,
b) used for an indication not included in the SmPC under the authorisation for that product, or
c) used to gain further information about the form of that product as authorised under the authorisation;

Non-Investigational Medicinal Product (NIMP)

Products which are not IMPs as defined above may be supplied to participants in a trial and used in accordance with the protocol.
For instance, some clinical trial protocols require the use of medicinal products such as concomitant or rescue/escape medication for preventive, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the participant. They may also be used in accordance with the protocol to induce a physiological response.
These medicinal products do not fall within the definition of investigational medicinal products and can be referred to as "non-investigational medicinal products" (NIMPs).

Pharmacovigilance (PV)

The pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects, of medicines. (Source: The Importance of Pharmacovigilance, WHO 2002)

Reference Safety Information (RSI)

The information used for assessing whether an adverse reaction is expected. This is contained in either the IB or SmPC.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any adverse event or adverse reaction that:

a) results in death
b) is life-threatening[1]
c) requires hospitalisation[2] or prolongation of existing hospitalisation
d) results in persistent or significant disability or incapacity
e) consists of a congenital anomaly or birth defect.
f) is otherwise considered medically significant by the investigator[3]

Comments:
[1]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 event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[2]Hospitalisation is defined as an inpatient admission. Pre-planned hospitalisation, e.g. for pre-existing conditions which have not worsened or for elective procedures, does not constitute a serious adverse event.
[3]Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Severity: The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

Sponsor(s)

The "individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial".

Suspected Serious Adverse Reaction (SSAR)

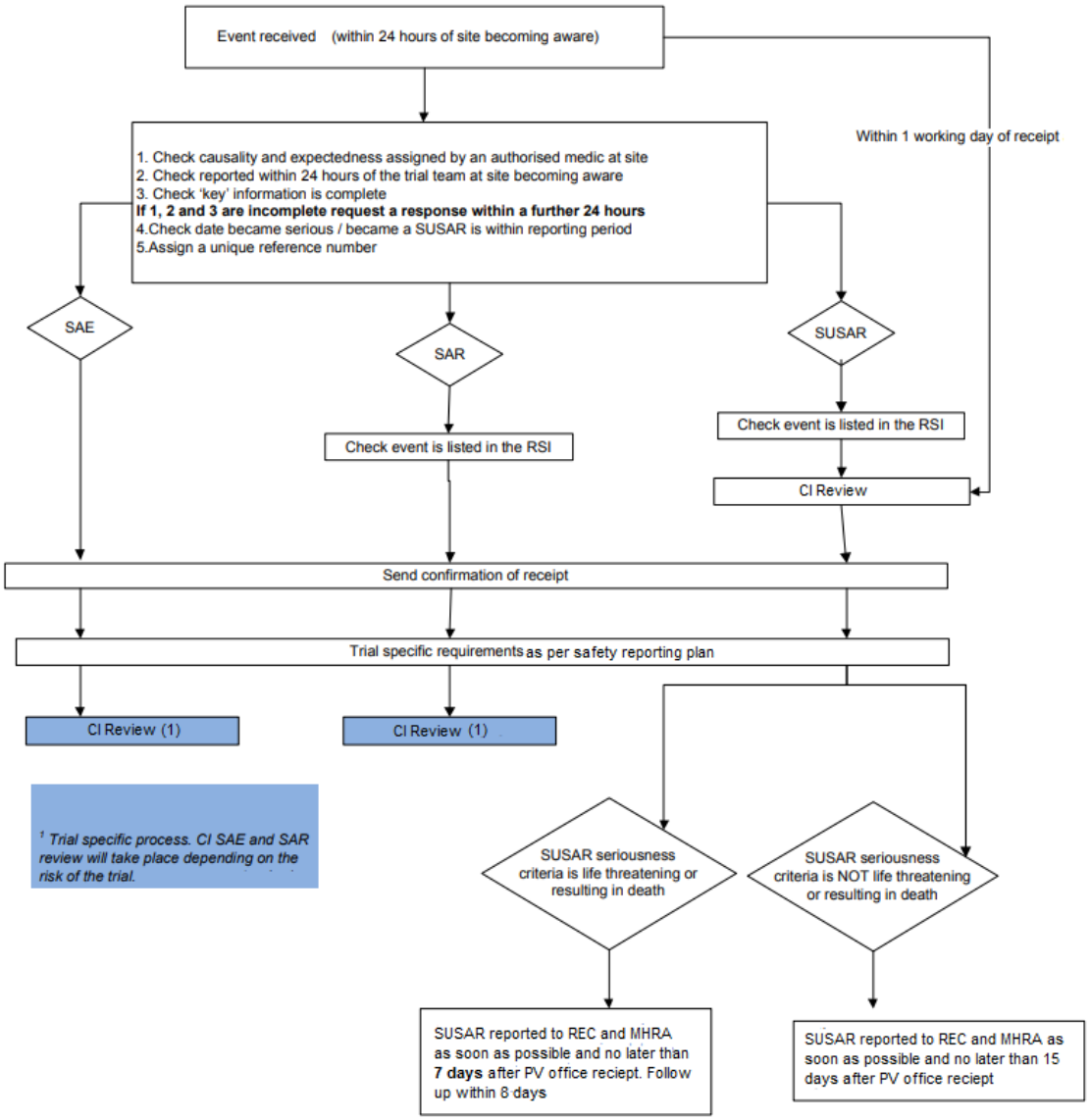
Any adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out

a) In the case of a licensed product, the SmPC for that product
b) In the case of any other investigational medicinal product, the IB relating to the trial in question.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out
a. In the case of a licensed product, the SmPC for
that product
b. In the case of any other investigational medicinal product, the IB relating to the trial in question.

Appendix 2


Event received (within 24 hours of site becoming aware)
Within 1 working day of receipt
1. Check causality and expectedness assigned by an authorised medic at site
2. Check reported within 24 hours of the trial team at site becoming aware
3. Check 'key' information is complete
If 1, 2 and 3 are incomplete request a response within a further 24 hours
4.Check date became serious / became a SUSAR is within reporting period
5.Assign a unique reference number
SAE
SAR
SUSAR
Check event is listed in the RSI
Check event is listed in the RSI
CI Review
Send confirmation of receipt
Trial specific requirements as per safety reporting plan
CI Review (1)
CI Review (1)
[1] Trial specific process. CI SAE and SAR review will take place depending on the risk of the trial.
SUSAR seriousness criteria is life threatening or resulting in death
SUSAR seriousness criteria is NOT life threatening or resulting in death
SUSAR reported to REC and MHRA as soon as possible and no later than 7 days after PV office reciept. Follow up within 8 days
SUSAR reported to REC and MHRA as soon as possible and no later than 15 days after PV office reciept