STANDARD OPERATING PROCEDURE 17
Safety

Part 1: Pharmacovigilance for Clinical Trials of Investigational Medicinal Products (CTIMPs)

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Revision Chronology:	Effective date:	Reason for change:
Version 4.0	30 Oct 2024	Biennial review: Biennial review: minor updates throughout text.
Version 3.0	31 August 2022	Biennial review: minor updates throughout text. Change of term 'Date deemed serious' to 'SAE start date' for improved clarity. Amendment to reporting timelines for SAEs to be considered with the context of the half-life of the IMP.
Version 2.1	7 May 2020	Urgent update via Governance Committee Approval: Addition of requirement to send SUSARs to relevant investigators taking part in the study.
Version 2.0	4 July 2019	Biennial review: Major re-write. Combined with information from part 3 to present whole pharmacovigilance process. Added more detail on scope of tasks and responsibilities for all delegated parties. Added a new triage process to be able to capture evidence of the checks on SAEs performed.
Version 1.6	1 August 2016	Biennial review: Minor clarifications to text. Web links and process flowchart updated.
Version 1.5	26 February 2014	Biennial review: Web links updated. Addition of information on safety reporting for international trials.
Version 1.4	1 December 2011	Update to annual safety reporting requirements. Additional information re: blinding and pregnancy in clinical trials
Version 1.3	1 September 2010	Addition of information re: new MHRA electronic SUSAR reporting system (section 3.3.4.1)
Version 1.2	29 January 2010	Biennial review. Web page links & CTCAE version number updated.
Version 1.1	25 January 2008	Format change. Clarification of reporting process.
Version 1.0	March 2006	

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1. Purpose and Scope

The purpose of part 1 of this Standard Operating Procedure (SOP) is to describe the process for pharmacovigilance where it has been formally delegated by the trial sponsor to Warwick Clinical Trials Unit (WCTU). In addition to the processes detailed in this SOP, there should be awareness for the reporting and contractual requirements for any external Sponsors.

Details on the safety reporting requirements for non-CTIMP (Clinical Trials of Investigational Medicinal Product) trials can be found in Part 2 of this SOP 'Safety reporting for trials other than CTIMPs'. Part 1 of this SOP should be read in conjunction with part 4 'Reference Safety Information (RSI)'.

2. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding or ECG result), symptom, or disease.
Adverse Reaction (AR)	All untoward and unintended responses to an IMP related to any dose administered**.** This is an AE for which there is reason to suspect that it may be *caused* by the administration of the IMP.
Serious Adverse Event and Serious Adverse Reaction (SAE or SAR)	An AE is considered 'serious' if it fulfils one of the following criteria: 1. Results in death, 2. Is life-threatening, 3. Requires hospitalisation or prolongation of existing inpatients´ hospitalisation, 4. Results in persistent or significant disability or incapacity, 5. Is a congenital anomaly or birth defect, 6. Requires medical intervention to prevent one of the above, or is otherwise considered medically significant by the investigator (e.g. participant safety is jeopardised). An SAE becomes an SAR if there is a potential for there to be a causal relationship to the administration of the IMP.
SAE/SAR Start Date	Sometimes referred to as Date Deemed Serious. The date that the AE fulfilled one or more of the 6 criteria that deems an event to be 'serious' as per the definition above.
Date Research Team Aware	The date that a member of the site or coordination centre research team are made aware of the occurrence of an SAE or SAR, whichever is earlier.
Causality	A medical assessment of whether an SAE has a possible causal relationship to the administration of the Investigational Medicinal Product (IMP).

Expectedness	An assessment as to whether the SAR is recorded in the current approved RSI or whether it is present at the same frequency and/or severity.
Reference Safety Information (RSI)	A list of previously reported Serious Adverse Reactions to an IMP. Typically contained within the Summary of Product Characteristics (SmPC) or the Investigator Brochure (IB).
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A suspected serious adverse reaction that is also unexpected i.e. the nature, frequency or severity of the event is not consistent with the applicable RSI. A SUSAR is therefore a reaction suspected of having a possible causal relationship with the IMP which has not previously been documented in the RSI.
Day zero (0)	The day that an SAE/R is reported to the WCTU by a member of the site or coordination centre research team. All reporting timelines stated in this document are calculated in calendar days from day 0.

3. Background

The Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031 detail the expectations for the adequate recording, evaluation and reporting of Adverse Events (AEs), Adverse Reactions (ARs), Serious Adverse Events/Reactions (SAE/Rs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) for CTIMPS. Failure to comply with the regulations is a criminal offence. It is important to monitor receipt of cumulative safety information for ongoing review of the risk/benefit profile of the Investigational Medicinal Product (IMP) in the context of the clinical trial.

You are also advised to refer to the University of Warwick's Research Code of Practice: https://warwick.ac.uk/services/ris/research-integrity/research_code_of_practice/

4. Procedure

4.1 Responsibilities

All staff working on CTIMPs must ensure that they are familiar with the processes contained within this document, and the reporting timescales required by law. The sponsor is responsible for pharmacovigilance and compliance with the regulations, however for University of Warwick Sponsored CTIMPs, pharmacovigilance activity is delegated to WCTU but key oversight is maintained by sponsor representatives in Research and Impact Services (R&IS). For externally sponsored CTIMPs any delegation of pharmacovigilance responsibilities should be made clear in the relevant agreements between the external sponsor and the University of Warwick. Consideration should also be made for additional reporting requirements to other bodies or third parties where it is appropriate or contractually stated.

Where WCTU are managing pharmacovigilance, the following delegation of tasks applies:

Chief Investigator (CI) *or delegate*:	• Causality assessment on behalf of the sponsor (this can be delegated to another medically qualified professional that is either independent or part of the trial team but they should be independent from the investigator site). • Support the Trial Manager/ Trial Coordinator (TM/TC) with the expectedness assessment of SARs.

	• To submit SUSAR reports to the MHRA & Research Ethics Committee (REC) within the timelines specified in this SOP. • Reporting of safety events to oversight committees • Regular monitoring of the risk benefit profile
Principal Investigator (PI) *or delegate(s)*:	• Recording AEs in the Case Report Form (CRF) in accordance with the approved protocol, • Reporting SAEs to WCTU via the route specified in the protocol within 24 hours of the date they become aware of the occurrence of an SAE. • Perform seriousness & causality assessment on any AEs
Quality Assurance (QA) Team:	• Perform initial triage checks on incoming SAEs • Support the TM/TC to conduct expectedness assessment of SARs against the approved RSI. • Maintain oversight of SUSAR expedited reporting to ensure it is done within the timelines specified in this SOP. • Maintain administrator rights for Individual Case Safety Report (ICSR) system
Trial Manager/Trial Coordinator:	• To check SAE/Rs according to the instructions in this SOP and liaise with investigator sites to obtain complete information about SAE/R reports received. • Conduct expectedness assessment in conjunction with the CI on SARs using the approved RSI. • Ensure systematic review of SAE/Rs is conducted at TMGs, with the review and any outcomes documented in the meeting minutes. • Immediately notify sponsor representative of all potential SUSAR reports. • Support CI to submit SUSAR reports • Organise data entry including Quality Control (QC) of SAE/Rs in a format that allows both cumulative monitoring by the TMG and DMC and inclusion in the Developmental Safety Update Report (DSUR) and any other reports required by third parties. • Ensure cover is in place to cover receipt, causality and expectedness responsibilities for periods of absence or University Closures.
Senior Project Manager (SPM):	• To ensure appropriate delegation of responsibilities with regards to pharmacovigilance for externally sponsored studies and to inform the QA team of requirements. • To ensure cover is in place should the Trial Manager/coordinator be unavailable.
R&IS:	• Organise oversight of SUSAR reporting via the University of Warwick Sponsorship and Oversight Committee in liaison with WCTU QA team.

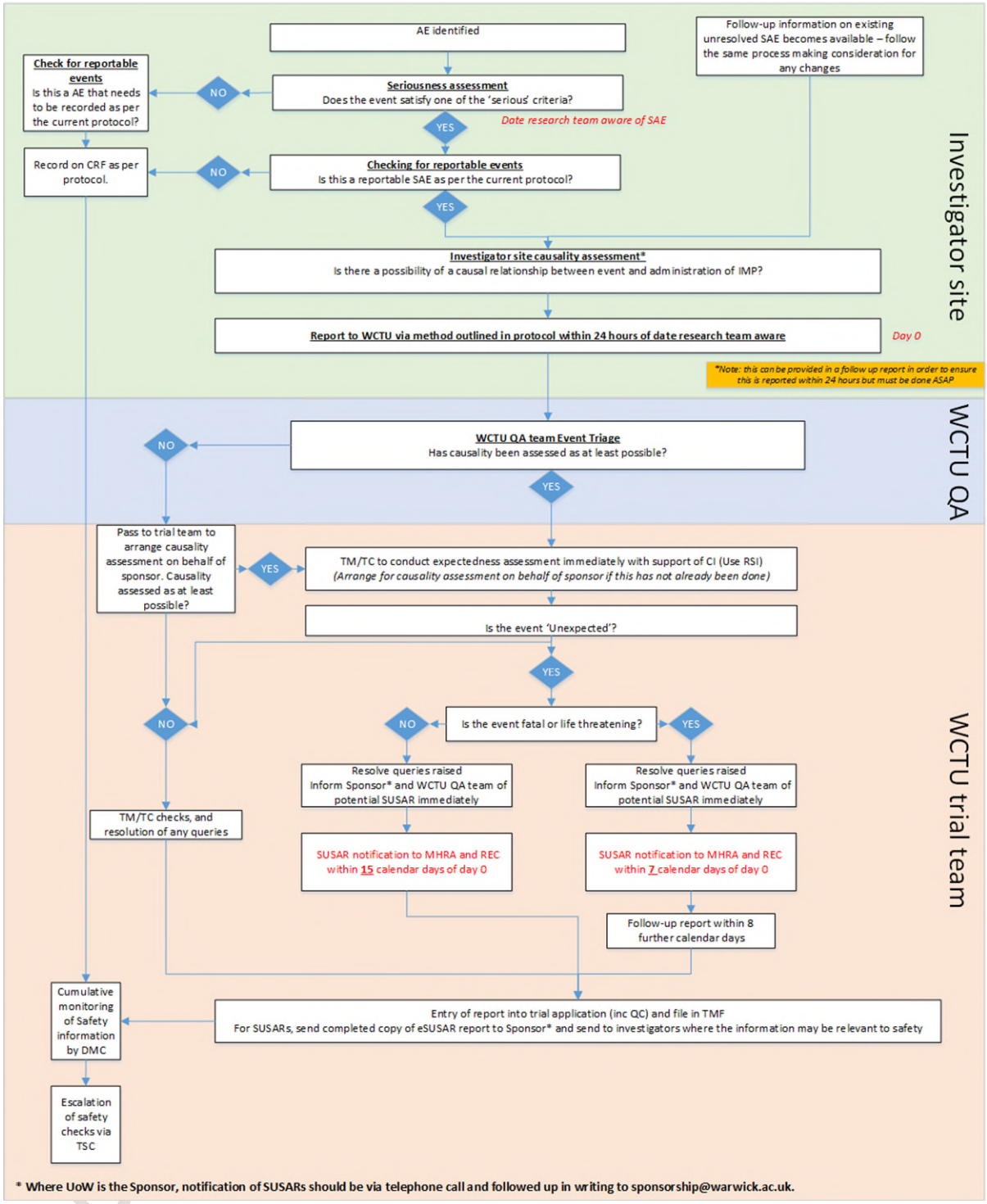
4.2 When?

AEs and SAE/Rs should be recorded, reported and expedited to the relevant bodies within the timelines specified by this SOP and relevant legislation. Safety information should continue to be monitored throughout the trial so that any change to the risk-benefit profile of the IMP can be acted upon quickly.

4.3 How?

The proposed procedures for assessing, recording, notifying and reporting of AEs should be agreed for each trial and explicitly detailed in the trial protocol. The trial protocol must be approved by the Health Research Authority (HRA), a REC, and the MHRA during the Clinical Trial Authorisation (CTA) assessment. Such procedures should also comply with the requirements set out in this SOP. Any trial specific processes that are required in addition to those detailed below, should ideally be contained with a Trial Specific Working Instruction which should be generated, reviewed and approved in line with SOP 34.

Figure 2 is a flow chart summarising the pharmacovigilance process in more detail. Further information relating to each element can be located below.



4.3.1 Identification of AEs and SAEs at investigator site:

- The start and end of the recording and reporting period for AEs and SAE/Rs should be defined in the protocol and usually includes events from the time the participant gave informed consent until the time-point defined in the protocol.
- At each trial visit, or trial assessment, adverse events that have occurred since the previous visit or assessment should be elicited from the participant or evaluated in the medical records by the PI or their delegate. The protocol for the clinical trial should state the mechanism by which participants will be asked about any AEs they may have experienced.

- The end of reporting should be driven by the half-life of the IMP. SAE/R reporting typically continues for at least 5 times the half-life of the IMP.
- Any worsening of current illness or new illness should be recorded as AEs in the medical notes at each visit. All AEs should be recorded unless there is justification in the protocol for not recording.

4.3.2 Seriousness assessment

An AE is considered 'serious' if it fulfils at least one of the following criteria:

1. Results in death,
2. Is life-threatening,
3. Requires hospitalisation or prolongation of existing inpatient's hospitalisation,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly or birth defect,
6. Requires medical intervention to prevent one of the above, or is otherwise considered medically significant by the investigator (e.g. participant safety is jeopardised).

Important notes: "*Serious*" and "*severe*" are not synonymous. "*Serious*" refers to a specific definition for the outcome of an event (see above), whilst "*severe*" refers to the intensity of an event (e.g. mild, moderate, severe). For example, it is possible to have a "severe" headache, but the headache itself is not a "serious" event.

The term *'life-threatening'* in the definition of a SAE refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which, hypothetically, might have caused death if more severe.

The term *'Disability'* is defined as a substantial disruption of a person's ability to conduct normal life functions.

The term *'Hospitalisation'* refers specifically to admission to a hospital ward for an overnight stay. Attendance at Accident and Emergency is not in itself serious unless there was a requirement for a medical intervention to prevent one of the other 'serious' outcomes from occurring.

4.3.3 Checking for reportable events

- It is possible under some circumstances for protocols to define some AEs that are not required to be recorded in the CRF and SAEs that do not require reporting to WCTU in the timelines defined by this SOP.
- Where certain AEs or SAEs will not be recorded or reported, they should be clearly defined and justified in the protocol making clear whether just the AE is non-reportable or whether the event remains non-reportable if it also meets one of the criteria for seriousness. Please note that events that are exempt from reporting are different to the list of expected events for assessment of expectedness of SARs.
- Justification for excluding some events from reporting may include:
  - AEs where the safety profile is already well established, and the IMP is being used within its licenced indication.
  - Events for blinded studies which could unintentionally compromise the integrity of the blind
  - SAEs which are commonly experienced because of the population or disease being studied rather than the intervention itself, e.g., anticipated events from disease progression.

SAEs that form an outcome for the trial do not need to be subject to expedited reporting by the site, however, details of such events must be included in the safety analysis by the DMC and form part of the annual Development Safety Update Report (DSUR) to the MHRA.

4.3.4 Causality assessment by the investigator site

Causality assessment is a medical judgement from a doctor's best knowledge of the patient, the event and the protocol intervention as to whether there is a possibility the event is related to the administration of the IMP.

WCTU uses a 5-point causality scale: 'definitely', 'probably', 'possibly', 'unlikely', 'unrelated'. Any SAE coded as definitely, probably, or possibly are considered to have a causal relationship to the participants involvement in the research.

An independent assessment of causality should also be done by the CI or their medically qualified delegate on behalf of the sponsor (see section 4.3.10).

There should be a clear declaration from the PI and CI (or their delegate) in the form of a physical or electronic signature. An email can be acceptable if it follows the guidance in G33 – Email Approval Guidance. A copy and pasted digital signature/image will not suffice.

4.3.5 Reporting to sponsor or WCTU

- SAE/Rs should be reported to the sponsor or to the delegated person at WCTU via the method detailed in the protocol, within 24 hours of becoming aware that an AE fulfilling the criteria for 'seriousness' has occurred. If there is any ambiguity regarding whether the event has met the criteria for 'seriousness' the best approach is to report to WCTU and to downgrade the event later when further information to clarify the situation is available.
- Where SAE/Rs are reported verbally or via another mechanism other than the CRF, a minimum amount of information should be captured: Trial Number (TNO), investigator site, 'Seriousness' category, brief details of the event, confirmation of when a written report is likely to follow.
- Verbal reports must be documented and followed up with a written report as soon as possible.
- The date of the verbal report is day 0 when considering compliance for expedited reporting.
- SAE/Rs may be reported to the QA team via the trial coordination team, and this should be done immediately upon being notified by the investigator site. Day 0 in these cases will be the date that WCTU receives this information and not necessarily the date it was given to the QA team.
- A written SAE report should follow the current template which can be requested from the QA team.
- On receipt of the initial report, the QA team must log this report on the SAE database. This should ideally be done on the day of receipt. and triage the event as detailed in section 4.3.7. The trial team may also need to track the status of the SAE to aid with follow-up to completion as per the Data Management Plan (DMP) or applicable working instruction.

4.3.6 Identification of SAEs via routine or triggered monitoring activities

- Where an SAE is identified from incoming Case Report Forms (CRFs), medical notes at monitoring/site visits or information provided by a participant or relative during a phone call, the investigator site should be notified immediately (same day) and asked to complete an SAE form and report to the coordinating centre as soon as possible.
- Day 0 for this event would be the day the information arrived at the coordinating centre or date it was identified in the medical records at site by the monitor. The date investigator aware for this event should be noted as the date of completion of the CRF on which it was identified or the date it was recorded in the medical notes as noted at the monitoring visit.
- The investigator site should then perform tasks as outlined in this SOP and protocol.
- Failure to report an SAE/R to the sponsor via the mechanisms stated in the protocol is a violation of the protocol and GCP and should be dealt with via the process outlined in SOP 31'Handling non-compliances, misconduct and serious breaches of GCP and/or study protocol'.

4.3.7 WCTU QA Team Event Triage

Upon receipt of an SAE report, a member of the QA team will check the following details on each report and document the outcome of the checks on an SAE triage form, this should be signed and dated and passed to the TM/TC or emailed directly. A unique SAE reference number will be allocated. The QA team will also triage for corrections to an original form received or on any follow-up forms.

All dates and actions/escalations, along with the key data from the SAE/R will be recorded in a database that can be accessed only by members of the QA team, WCTU senior management and sponsor representatives from the University of Warwick. Each report (verbal or written) will be logged and triaged according to the criteria below

Check	Action or escalation
Does the report fulfil the criteria for 'seriousness'?	If no, pass to TM/TC to liaise with site. WCTU will never downgrade an event without the permission of the site, but TM/TC should confirm this is not a reporting error. If error confirmed, QA team should remove from SAE log. Trial team to retain documentation of decision in Trial Master File (TMF).
Is the date investigator aware, within 24 hours of day 0?	If no, liaise with the TM/TC. Sites should be reminded of the requirement and non-compliances recorded. Persistent late reporting should be monitored and escalated as per SOP 31. Persistent late reporting would be considered a violation of GCP and recorded as per SOP 31.
Is the SAE/R start date correct according to the information and sequence of events described in the report narrative?	If no, pass to TM/TC to liaise with site to obtain correct information. TM/TC to inform QA of any amendments. TM/TC to retain audit trail of amendments.
Is the current outcome listed?	If no, pass to TM/TC to liaise with site to obtain correct information. TM/TC to inform QA of any amendments. TM/TC to retain audit trail of amendments.
Any obvious contradictions to the severity assessment with the remainder of the event details? E.g. severity is life-threatening but seriousness listed as hospitalisation only.	If yes, pass to TM to liaise with site. TM/TC to inform QA of any changes. QA to amend log. TM to retain audit trail of amendments.
Has causality been assessed and signed off by investigator site?	If no, TM/TC to liaise with site to obtain this information. QA will provide a timeline for when this needs to be confirmed in order to comply with any expedited reporting that might be required if a possible causal relationship was suspected, and a subsequent expectedness assessment deemed it unexpected.

Upon completion of triage, the QA team must pass the triage form to the TM/TC to initiate the independent causality assessment on behalf of the sponsor and to conduct an expectedness assessment (where causal relationship is deemed possible by either the investigator site or sponsor) and to follow-up any queries identified on the report. This can be done concurrently with the QA triage to facilitate swift resolution. See sections 4.3.10 and 4.3.11 for more details.

4.3.8 Cover arrangements for QA triage

During periods when the university has statutory/customary closures, the QA team will arrange for the QA resource email account to be checked regularly. If none of the QA team are available, they should ensure cover is available and responsibilities are clearly communicated.

4.3.9 Checking and entry of SAEs by the trial team

All SAE/Rs should be assessed for causality and expectedness on behalf of the sponsor (see sections 4.3.10 and 4.3.11). In all cases where causality assessment by the site or by the sponsor is confirmed to be at least possibly related, the TM/TC must conduct an expectedness assessment on behalf of the sponsor with support from the CI if necessary. Independent causality and expectedness assessments should be reported back to QA as soon as possible. Expectedness assessments are not required for events assessed to have no causal relationship (unlikely or unrelated).

The TM/TC should action any queries raised on the QA triage form and perform and document the additional trial specific checks detailed in the table below. These checks should be done at the point of triage and not at the point of entry unless this will be done concurrently.

Confirm the event is reportable according to the protocol that was implemented at the time of the event	If not, liaise with site to establish if this was a reporting error. Liaise with QA to downgrade the event in the SAE database if required. Keep audit trail of all decisions.
Compliance checks – is the dose, strength and type of IMP correct? Are dates of administration correct according to schedule?	Overdose of IMP is an immediate safety concern and a possible serious breach. Any non-compliance with IMP will usually constitute a violation and Immediate contact with the site is required to establish correct information – see SOP 31 'Deviations, Violations, Misconduct and Serious Breaches of GCP and/or Study Protocol For actions and escalation if any non-compliance has occurred.
CTCAE term and SOC appropriate and valid? *(or other relevant coding system)*	If no, TM/TC to liaise with site. This will need to be correct in order to be able to perform expectedness assessment where a possible causal relationship is reported. TM to retain audit trail of amendments.
Complete data?	If no, TM to liaise with site. TM to retain audit trail of amendments.
Withdrawal	If the participant has withdrawn from trial treatment as a result of this event, prompt the site to complete the necessary paperwork.
Appropriate delegation of person assessing causality at investigator site	Must be medically qualified and present on delegation log with code for attributing causality to SAEs, if not, needs to go back to site immediately for countersignature and reassessment.

If SAE reports come via another mechanism other than direct entry onto the CDMS, the TM should coordinate the entry of SAE reports in a timely way. There should be QC procedures in place to demonstrate the accuracy of information entered. This should be defined in the trial Data Management Plan (DMP) or Monitoring Plan (MP). See SOP 19 'Quality Control' for more information. For SAEs entered directly onto the CDMS, consideration for notification systems should be made to ensure timely notification to the appropriate reviewers.

4.3.10 Causality assessment on behalf of the sponsor

Assessment of causality is required on behalf of the sponsor in addition to the investigator site. The two assessments should be independent, and the sponsor is not permitted to downgrade or influence the causality assessment made by investigator site. In situations where there is a disagreement, the worse case scenario should be used to determine whether to expedite or not. Any differences in opinion should be provided with the SUSAR report. This causality assessment has to be done by a representative of the sponsor who is medically qualified. This is typically the CI but can be someone else within the trial team or an independent person who is medically qualified. The documentation of this delegation must be clear on a trial-by-trial basis. They must be independent of the investigator site. The role here is to assess causality on behalf of the sponsor using their best knowledge of the treatment and the protocol. The assessment should be recorded using the SAE evaluation form or an email confirmation from someone who has the appropriate responsibility. If email confirmation is used, it should be clear in the body and title of the email to which report the evaluation is related and these should be stored with the SAE to which they relate in the TMF.

4.3.11 Expectedness assessment on behalf of the sponsor

Expectedness assessment only needs to be completed if there is a possibility of a causal relationship with the IMP. Expectedness is not a clinical judgement, and assessment should compare the event with the RSI that was current on the date that the event was deemed to fulfil the criteria for 'serious' (for more information on the management of RSI, see part 4 of this SOP). A delegate of the sponsor should perform this assessment. This should be done by a representative of the sponsor who has been appropriately delegated but does not necessarily need to be medically qualified. This will typically be done by the TM/TC with support from the QA team and the CI.

SARs which are not listed in the RSI or SARs that are reported in a more severe or specific form than is listed in the RSI are considered to be unexpected and should be reported as SUSARs.

Example 1: The RSI states that Hypertension is an expected reaction, however the SAR is reported as 'Hypertensive crisis' this is more severe than is listed in the RSI and would therefore constitute a SUSAR.

Example 2: The RSI states that Supraventricular Cardiac Arrhythmia is an expected reaction, however, the SAE is reported as 'Atrial fibrillation'. This is a more specific condition and would therefore constitute a SUSAR.

Any potential SUSARs should be reported to the Sponsor immediately by the TC/TM. Where UoW is the sponsor, the Sponsor's Office in R&IS should be informed verbally via telephone and followed up in writing to sponsorship@warwick.ac.uk. Potential SUSARs will be reported by the Sponsor's Office to the Chair of the Sponsorship and Oversight Committee. Any concerns or queries raised will be directed back to the Trial Team.

4.3.12 Expedited reporting of SUSARs

SAEs that have been assessed by the investigator and/or Sponsor as both having a causal relationship to the administration of the IMP and are unexpected according to the RSI (i.e. a SUSAR), must be reported to the REC and MHRA within set timelines of seven days for a fatal or life threatening event and within 15 days for all other events. Accounts for reporting SUSARs are made in the CI's name and is typically reported by the CI on behalf of the sponsor with support from the TM/TC and QA team who will monitor timelines and ensure compliance.

Reporting

a SUSAR to the Competent Authority (MHRA for UK) is done via the ICSR submissions system: https://icsrsubmissions.mhra.gov.uk/login. It is a good idea to request a list of medications from the site at the point you suspect a SUSAR as this can be time consuming to obtain and it will be necessary for the SUSAR report.

WCTU has been delegated by the UoW Sponsor's Office to register details of the Institution and nominated a representative from the QA team as the main Administrator of the ICSR system. For each CTIMP where pharmacovigilance and the submission of SUSAR reports has been delegated to WCTU, the CI should delegate a member of the trial team to register on the system and report any SUSARs that occur if they are unable to do this task on behalf of the sponsor.

The CI or their delegate should promptly notify all concerned investigators/institutions of findings that could adversely affect the safety of the trial subjects and should expedite the reporting of all SUSARs to all concerned investigators/institutions.

Any follow-up reports should be added to the report as they are received.

For more information, visit the MHRA safety reporting web pages:
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

Copies of all these reports should be filed in the TMF.

4.3.13 Follow-up Reports

All SAE/Rs should be followed up until clinical recovery is complete or until the participants status is unlikely to change.

Follow-up reports should be submitted in any of the following situations:

- Resolution is reached or change in outcome is confirmed
- Additional information comes to light
- There is an increase in severity
- There is a change to the causality assessment

Follow-up SAE/Rs should be dealt with via the same process described above. Any changes to an event should be noted and, consideration should be given to reassessment of the event. When additional information comes to light, the causality should be reassessed and documented as per the sections above. Seriousness assessment should remain unchanged on follow-up reports as this relates to the point of reporting. Any changes to severity or outcome are captured in these sections of the report so that a narrative of the course of the event is captured.

4.3.14 Blinded IMP

Where possible, the blind should be maintained. However, if a SAE is deemed to be a SUSAR, the treatment code for the participant concerned must be broken before reporting the event to the MHRA and REC.

The breaking of the code should be recorded along with the reasons on the CRF, any unblinding reports should be filed in the patient file and a record kept for analysis by the appropriate steering committees. If after unblinding the product administered to the participant is the **placebo** then a consideration should be made as to whether the event was a reaction to a component of the placebo before determining whether or not it still satisfies the criteria for a SUSAR. Where multiple events relating to a placebo have been reported, consideration should be given to reporting these events to all relevant parties.

To reduce potential for bias to occur in the remaining trial participants following an unblinding event, a procedure should be in place to cover how unblinding is handled.

4.3.15 Cumulative monitoring of safety information

Cumulative safety information (SAE/Rs and AEs) may be presented at Trial Management Group (TMG) Meetings as determined by the Risk Assessment and Monitoring Plan. The following should be evaluated, and the outcome of the evaluation recorded:

- AEs or SAE/Rs reported in a severity or frequency that is unexpected for the trial population that may change the opinion of causality
- Unresolved SAE/Rs requiring escalation
- Systematic issues including, regular late reporting of SAE/Rs, unusual trends in event types
- Vast differences between reporting levels at sites – sites that have not submitted any SAEs should be considered in the context of the trial and the context of the number of participants.
- Potential over-reporting by site(s).

Cumulative safety information must be monitored by the DMC who will also consider accumulating safety information for each arm of the trial. Any safety concerns will be escalated via the Trial Steering Committee.

4.3.16 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive method. Guidance on suitable contraceptive methods can be found at: https://www.gov.uk/government/publications/common-issues-identified-during-clinical-trial-applications/common-issues-clinical

A trial participant must be advised to notify the PI or investigator site team immediately if they become pregnant during the trial (unless pregnant women are the population of study). The Investigator must then report any pregnancy to the WCTU QA Team or the WCTU trial team who should then notify the QA team via an appropriate CRF. Any pregnancy should be followed up and any complications recorded as an AE. If the IMP is known to have the potential for transfer to the foetus in seminal fluid, then it may be necessary to follow up the pregnant partners of any trial participants as long as there is consent from the partner to do so. If the infant has a congenital anomaly/birth defect, this must be reported and followed up as a SAE. Where pregnancy is an exclusion criterion, the participant should be withdrawn from trial treatment and followed up in accordance with the protocol.

Appropriate/acceptable contraceptive methods should be clearly documented in the trial protocol and Participant Information Sheet.

List of abbreviations

AE/AR	Adverse Event /Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSUR	Development Safety Update Report
EEA	European Economic Area
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigator Brochure
ICSR	Individual Case Safety Report
IMP	Investigational Medicinal Product
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MP	Monitoring Plan
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
R&IS	Research and Impact Services
RSI	Reference Safety Information
SAE/SAR	Serious Adverse Event/Reaction
SOC	System Organ Class
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SPM	Senior Project Manager
SSDL	Site Signature and Delegation Log
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TM/TC	Trial Manager/Trial Coordinator
TNO	Trial Number
TSC	Trial Steering Committee
UoW	University of Warwick
WCTU	Warwick Clinical Trials Unit