UNIVERSITY OF WARWICK

STANDARD OPERATING PROCEDURE 17 Part 2

Safety

Safety Reporting for Clinical Trials *other than* those of Investigational Medicinal Products

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Review Lead:	Greg Scott, QA Support Officer, WCTU
WCTU Reviewers:	Helen Bradley, SPM, WCTU Aminul Haque, Research Fellow, WCTU Kerry Raynes, TM, WCTU
Sponsor Reviewers:	Mathew Gane, Research Governance & QA Manager, R&IS
WCTU approval:	Natalie Strickland, Head of Operations, WCTU
Sponsor approval:	Carole Harris, Associate Director Research Culture, Governance and Compliance, R&IS

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Version 5.0	30 November 2026	Biennial review: New SAE Reconciliation section. Minor amends: to events that may be excluded from reporting; and to responsibilities. Tidying of text for clarity. Move to new SOP template.
Version 4.0	13 November 2024	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.
Version 2.1	7 May 2020	Urgent update via Governance Committee Approval: Addition of requirement to send related and unexpected SAEs 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 safety reporting 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. Information regarding SAEs identified via monitoring procedures.
Version 1.5	1 August 2016	Biennial review: Minor text amends, reporting process flowchart updated. Change to new format.
Version 1.4	14 April 2014	Biennial review: Web links updated. Minor clarifications to text.
Version 1.3	1 March 2012	Biennial review: clarification to text and formatting changes only
Version 1.2	15 February 2010	Biennial review: Updated CTCAE version number and information on trials of devices.
Version 1.1	31 January 2008	Format change. Clarification of reporting process.
Version 1.0	March 2006	

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1 Purpose and Scope

The purpose of this SOP is to describe the process for safety reporting in research studies that do not involve an IMP. This applies to studies sponsored by the UoW or are externally sponsored and managed through WCTU and where safety reporting has been formally delegated by the trial sponsor. In addition to the processes detailed in this SOP, there should be awareness for the reporting and contractual requirements for any external Sponsors or organisations involved in the development, manufacture, supply or support of the intervention (e.g. the manufacturer of a device used within the intervention), especially where expedited reporting may be required.

Details on the safety reporting requirements for CTIMPs can be found in Part 1 of this SOP.

2 Acronyms

AE	Adverse Event
ADE	Adverse Device Effect/Event
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DMP	Data Management Plan
GCP	Good Clinical Practice
HRA	Health Research Authority
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
MP	Monitoring Plan
PI	Principal Investigator
PROMs	Patient Reported Outcome Measures
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
R&IS	Research and Impact Services
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event/Reaction
SOC	Sponsorship and Oversight Committee
SOP	Standard Operating Procedure
SPM	Senior Project Manager
SSDL	Site Signature and Delegation Log
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
USADE	Unanticipated Serious Adverse Device Effect
WCTU	Warwick Clinical Trials Unit

3 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation participant taking part in health care research, which does not necessarily have a causal relationship with the research. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding or ECG result), symptom, or disease that occurs during the time a participant is involved in the study, *whether or not* it is considered to be related to the intervention. AEs are recorded to support monitoring of safety signals throughout the lifetime of the trial.
SAE and Related SAE	An AE is considered 'serious' if it fulfils one or more 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 a related SAE if there is a potential for there to be a causal relationship to administration of any study procedure. SAEs are reported to enable further description of the event and so the event can be evaluated in relationship to the trial intervention(s).
SAE Start Date	Sometimes referred to as Date Deemed Serious. The date that the AE fulfilled one or more of the six 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 coordinating centre research team is made aware of the occurrence of an SAE. Where SAEs are elicited from the return of participant questionnaires and do not come via an investigator site, the Date Investigator Aware should be the date that the coordinating centre informs the investigator site.
Causality	A clinical or medical assessment of whether the SAE has a possible causal relationship to administration of any of the study procedures.
Expectedness	An assessment as to whether a related SAE has been previously documented as being related to any of the research procedures. Previously documented 'expected' events should be available and listed in the study protocol or in relevant literature.
Day zero (0)	The day that an SAE 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.

4 Background

For clinical studies involving only CE marked medical devices, food supplements or other non-medical therapies (such as surgical or physiotherapy interventions) the processes for safety reporting in clinical trials are not covered by regulations, but the accurate and timely reporting of AEs in all clinical trials is a requirement of GCP.

It is important to monitor receipt of cumulative safety information for ongoing review of the risk-benefit profile of the research procedures being administered.

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/

5 Responsibilities

All staff working on clinical research studies must ensure that they are familiar with the processes contained within this document, and the reporting timescales. The Sponsor's Office in R&IS is responsible for safety reporting related to UoW sponsored studies. Where a UoW-sponsored research study is being managed by WCTU, this activity is delegated to WCTU and key oversight is maintained by the Sponsor's Office.

For externally sponsored research studies managed by WCTU, any delegation of safety reporting responsibilities should be made clear in the relevant agreements between the external sponsor and the UoW. Consideration should also be made regarding additional reporting requirements to other bodies or third parties where it is appropriate or contractually stated.

Where safety reporting responsibilities are delegated to WCTU on behalf of the sponsor, the following delegation of tasks applies:

CI *or delegate:*	• Causality assessment on behalf of the sponsor (this can be delegated to another appropriately trained medical or clinical professional). *The assessor must be independent of the investigator site*. • Support the TM/TC with the expectedness assessment of related SAEs using the approved protocol. • To submit reports to the REC where there is a related and unexpected SAE. This task can be delegated to the TM/TC if appropriately documented. • Reporting safety events to oversight committees. • Regular monitoring of the risk-benefit profile of the study.
PI *or delegate(s):*	• Recording AEs in the 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 and causality assessment for any AEs.
QA Team:	• Perform initial triage checks on incoming SAE. • Support the TM/TC in seeking completion of required assessments for SAEs in line with the approved protocol. • Maintain oversight of expedited reporting of unexpected and related SAEs to ensure it is done within the timelines specified in this SOP. • Provide oversight reports to SOC.
TM/TC:	• To check SAEs according to the instructions in this SOP and liaise with investigator sites to obtain complete information about SAE reports received. • Oversee the timely completion of SAE reports where the coordinating centre team have this responsibility (see section 7.2.2). • Conduct expectedness assessment in conjunction with the CI on related SAEs. • Ensure regular and consistent review of SAEs are conducted at TMGs, with the review and any outcomes documented in the meeting minutes.

	• Immediately notify UoW Sponsor's Office of all potential unexpected and related SAE reports. • Ensure cover for receipt and assessment of SAE reports is in place for periods of absence or University closures. • Ensure fulfilment of contractual requirements for reporting to co-sponsors, external sponsors, or other parties.
SPM:	• To ensure appropriate delegation of responsibilities with regards to safety reporting for externally sponsored studies and to inform the QA team of requirements. • To ensure cover is in place should the TM/TC be unavailable.
R&IS:	• Organise oversight of expedited reporting via the UoW SOC in liaison with WCTU QA team.

6 When

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

7 How

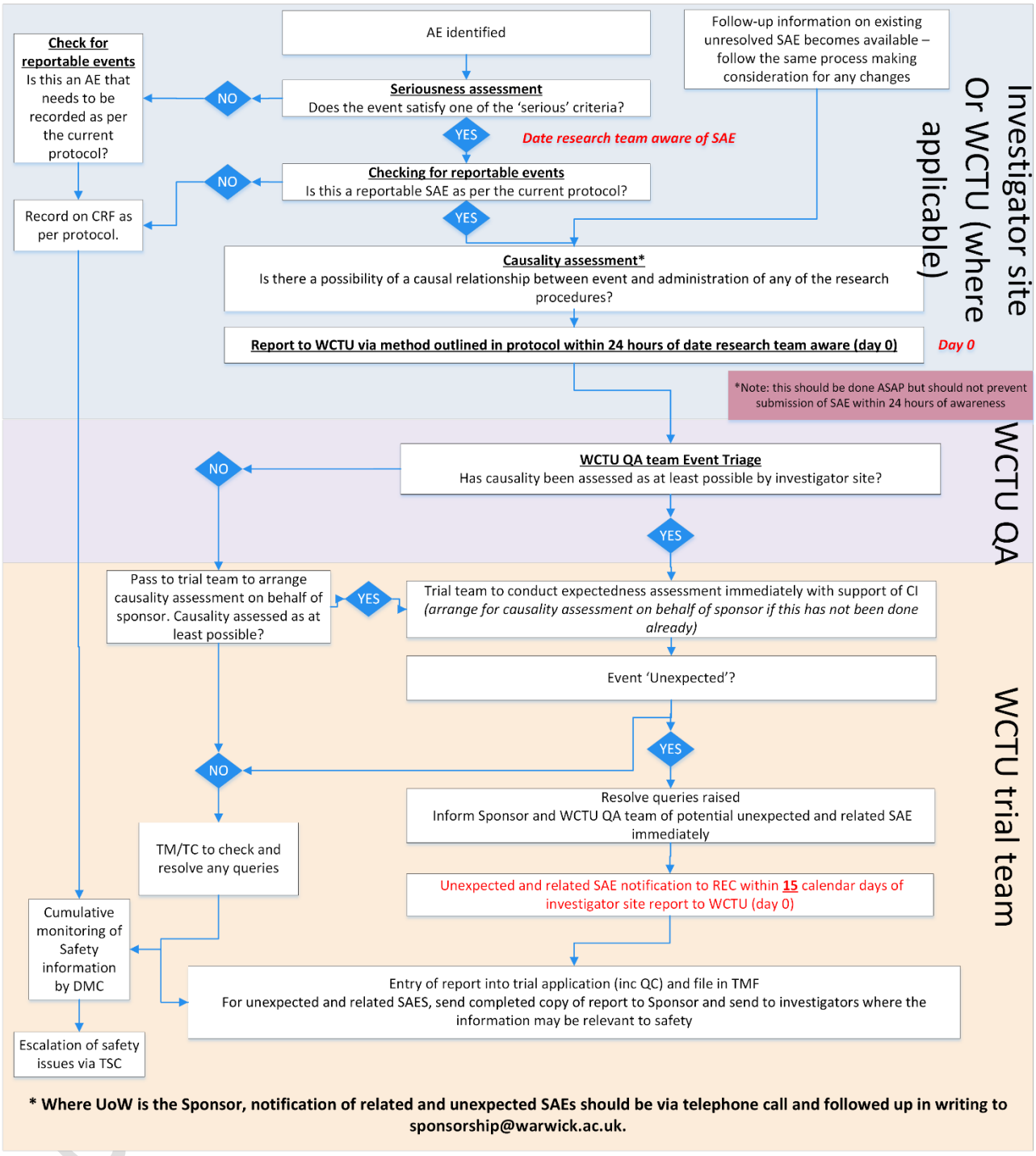
The proposed procedures for assessing, recording, and notifying AEs and reporting of SAEs should be agreed for each trial and explicitly detailed in the trial protocol. The trial protocol must be approved by the HRA and REC. Such procedures should also comply with the requirements set out in this SOP.

Any trial specific processes that are required in addition to those detailed below, should be contained with a Trial Specific Working Instruction which should be generated, reviewed and approved in line with SOP 34.

Any deviation from safety reporting processes in the protocol, this SOP or GCP should be recorded as a non-compliance. For further details see SOP 31 (Handling non-compliances, research misconduct and serious breaches of GCP and/or Study Protocol).

Below is a flow chart summarising the safety reporting process in more detail for studies managed through WCTU. Further information relating to each element can be located below.

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7.1 Identification of AEs and SAEs at investigator site:

The start and end of the recording and reporting period for AEs and SAEs should be defined in the protocol and usually include events from the time the participant gave informed consent until the time-

point defined in the protocol. Rationale should be provided in the protocol for the reporting period selected.

At each study visit, or study 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 study should state the mechanism by which participants will be asked about any AEs they may have experienced.

Any worsening of pre-existing illness or new illness should be recorded as AEs at each visit.

All AEs should be recorded unless they are detailed in the protocol as not required. If an AE meets the criteria for 'Serious' and is reportable, the AE need not be recorded on the CRF as this could lead to being counted twice in the analysis.

7.2 Identification of SAEs via other means

Potential SAEs may be identified by the coordinating centre rather than the investigator site via activities such as data cleaning or during central/remote/on-site monitoring. There are situations where review of PROMs, or other data collected from participants, may also identify the occurrence of an SAE and they should be reported in line with the following sections. Note if non-serious AEs are identified via these activities these should also be followed up with the investigator site or CI as required by the protocol to ensure they are recorded in the CRF where required.

7.2.1 Identification of SAEs via routine or triggered monitoring activities

Where an SAE is identified from incoming CRFs, medical notes at monitoring/site visits or information provided by a participant or relative during a phone call or email, 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 the investigator became aware of 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.

The investigator site should continue to perform tasks as outlined in this SOP and the protocol.

7.2.2 SAEs identified directly from participants

Where an SAE is identified directly from a participant e.g., via a PROM, questionnaire, or via a telephone call or email, that does not go via an investigator site, the investigator site should be informed as soon as possible and asked to complete an SAE form if possible. The date the researcher became aware of this event would be the date it was highlighted by the coordinating centre. This will then need to be reported to the Sponsor's Office/WCTU team within 24 hours in accordance with the process detailed in the protocol. In these cases, the seriousness assessment should be confirmed by site prior to form completion.

If the participant is no longer under the care of the investigator site or the trial is set up in a way that no investigator sites are involved, it is not possible to highlight to the site to action and assess the event, then the SAE form can be completed by the coordinating centre themselves. There should be someone clinically or medically qualified to perform a causality assessment of the event. This person should have knowledge of the protocol but ideally be independent of trial conduct and management to reduce any bias or conflict of interest.

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Where an investigator site is a GP surgery or another primary care service, SAEs may need to be completed by the coordinating centre to ensure timely reporting. If further information is required in these cases, trial staff can contact the participant if there is consent in place to do so or the activity is described in the participant information sheet.

SAEs reported by the coordinating centre should be the last resort as this method does not allow causality to be assessed by someone who is knowledgeable about both the study procedures and the participant. In this situation, the date the investigator became aware would be the date of arrival of this information into the coordinating centre, this would also be day 0. If from the information received, further information is required to ascertain if it fulfils the criteria for 'seriousness', it should be treated as an SAE until any information is received to the contrary. If the resulting information suggests the event is not 'Serious' then the event can be downgraded.

7.3 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 medical intervention to prevent one of the other 'serious' outcomes from occurring.

7.4 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 the sponsor (or to WCTU for WCTU managed studies) 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.

Please note that events that are exempt from reporting are different to the list of expected events for assessment of expectedness of related SAEs.

Justification for excluding some events from reporting may include:

- AEs where the safety profile is already well established

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- 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. Examples include death from progression of the disease where this forms an outcome for the study or hospitalisation for an event which forms an outcome for the study.

7.5 Causality assessment by the investigator site

Causality assessment is a clinical judgement from the clinician's best knowledge of the patient, and the event as to whether there is a possibility that it is related to the administration of any of the research procedures defined in the protocol. This should be done by the PI or a delegate that is medically or clinically trained. This will depend on the nature of the study and the appropriate expertise required. If the PI has delegated this activity, it should be clear from the SSDL.

WCTU use a 5-point causality scale: 'definitely', 'probably', 'possibly', 'unlikely', 'unrelated'. Any SAE coded as definitely, probably, or possibly are considered to have a possible causal relationship.

There should be a clear declaration from the PI (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 will not suffice.

An independent assessment of causality should also be done by the CI or clinical delegate on behalf of the sponsor (see section 7.10). This causality assessment is independent of the Investigator site's causality assessment.

7.6 Reporting to the sponsor or WCTU

SAEs should be reported to the sponsor or to the QA team at WCTU (if it is a WCTU managed study). This should be done via the method detailed in the protocol within 24 hours of becoming aware of an AE that fulfils the criteria for 'seriousness'. If there is any ambiguity regarding whether the AE has met the criteria for 'seriousness' the best approach is to report to the Sponsor/WCTU and downgrade at a later date.

Where SAEs are reported verbally or via another mechanism other than the CRF, a minimum amount of information should be captured: 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 receipt of a verbal report will constitute day 0 when considering compliance for expedited reporting.

For WCTU managed studies, SAEs must be reported to the QA team. This can be done directly from the investigator site or via the trial team. Where the trial team receive the information first, they must immediately report to the QA team. Day 0 in these cases will be the date that WCTU trial team receives this information and not that date it was given to the QA team.

- A written SAE report should follow the current templates, T51 – T57.
- On receipt of the initial report, the report should be logged on the SAE database immediately by the WCTU QA Team and triaged as detailed in section 7.7. The trial team may also need to track the status of the SAE to aid with follow-up to completion as per the DMP or applicable working instruction.

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7.7 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 or sent via email. 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 will be recorded in a database that can be accessed only by members of the QA team, WCTU senior management and sponsor representatives from UoW. 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 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 TMF.
Is the date investigator aware, within 24 hours of the notification/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 start date correct according to the information and sequence of events described in the event and in any relevant CRFs?	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 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

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	suspected, and a subsequent expectedness assessment deemed it unexpected.

** Where an SAE has come directly from a participant/relative and sending back to an investigator site for clarification is not possible, further information can be sought from the GP surgery, participant or relative to aid completion, but only where this is appropriate.*

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 7.10 and 7.11 for more details.

7.8 Cover arrangements for QA triage

During periods when the university has customary closures, the QA team will arrange for the QA resource email account to be checked regularly.

7.9 Checking and entry of SAEs by the trial team

For WCTU managed studies, 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.

Check	**Action or escalation**
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 in the SAE database if required. Keep audit trail of all decisions.
Complete data?	If no, pass to 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 or clinically qualified (depending on the nature of the study) 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 your DMP or 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.

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7.10 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 the investigator site. Where the investigator and sponsor causality assessments differ, the assessment resulting in the highest reporting requirement should be used. Therefore, if either assessment concludes that the SAE is related to a study procedure, the event should proceed to an expectedness assessment. Any differences in opinion should be provided in the expedited report, if required.

This causality assessment must be done by a representative of the sponsor who is medically or clinically qualified (dependent on the nature of the study). This is typically the CI but may be delegated to another member of the trial team or an independent assessor. Such delegation must be documented on a trial-specific basis. The individual performing the sponsor assessment must be independent of the investigator site.

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/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. There should be a clear declaration from the 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 will not suffice.

7.11 Expectedness assessment on behalf of the sponsor

Expectedness assessment is only required if at least one causality assessment (investigator or sponsor) identifies a possible causal relationship with a study procedure.

Expectedness is not a clinical judgement and assessment should compare the event with a pre-defined list of events that have been previously documented to have occurred in relation to the study procedures being studied. This list should ideally be located in the current protocol. The assessment should be done by a representative of the sponsor who has been appropriately trained but does not necessarily need to be medically qualified. For WCTU studies this should be done by the TM/TC with support from the CI.

Related SAEs which are not listed in the protocol as expected events or related SAEs that have been reported in a more severe or specific form than is listed in the protocol should be treated as unexpected.

Any potential related and unexpected SAEs should be reported to the sponsor as soon as is practically possible. Where UoW is the sponsor, the sponsor representative at R&IS should be informed verbally via telephone and followed up in writing to sponsorship@warwick.ac.uk. Potential related and unexpected SAEs will be reported by the Sponsor's Office to the Chair of the SOC. Any concerns or queries raised will be directed back to the Trial Team.

7.12 Expedited reporting of unexpected and related SAEs

SAEs that are considered related (based on either the investigator or sponsor causality assessment) and are unexpected according to the protocol must be reported to the REC within 15 calendar days from day 0. This is typically done by the CI on behalf of the sponsor. Notification of such events to the REC should be done using the appropriate form which can be found here: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/.

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The form should be completed electronically, printed and signed by the CI. The signed form should be scanned and submitted via email to the REC and sponsor and a copy saved in the TMF. If the CI is absent/unavailable, the responsibility for signing SAE reports should be delegated to an appropriate designee.

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 related and unexpected SAEs to all concerned investigators/institutions.

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

7.13 Follow-up Reports

All SAEs 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 another 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 SAEs should be dealt with via the same process described above. Where additional information comes to light, both the PI and the CI (or their delegates) must review this information and consider whether the causality should be reassessed. Reassessment of causality should be documented as per the sections above. Any changes to severity or causality should be noted and where there are changes to the causality assessment, consideration should be given to reassessment of expectedness, if relevant. 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.

7.14 Blinded studies

Where possible, the blind should be maintained. However, if an SAE is deemed to be unexpected and related, the treatment code for the participant concerned may need to be broken before reporting the event to the REC but this may not always be necessary. If unblinding is required, it 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 oversight committees.

If after unblinding the participant has been allocated to a control group where no research procedures have been administered, this may not satisfy the criteria for an unexpected and related event and may not require expedited reporting. It is the CI's responsibility to report such cases at their discretion.

For more information on managing blinding and unblinding in research studies refer to SOP 41 (Blinding and Unblinding in Research Studies).

7.15 Cumulative monitoring of safety information

Cumulative safety information (SAEs and AEs) should be presented at TMG meetings (the regularity of which should be determined by the Risk Assessment and MP). The following should be evaluated and the outcome of the evaluation recorded:

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- AEs or SAEs reported in a severity or frequency that is unexpected for the trial population that may change the opinion of causality
- Unresolved SAEs requiring escalation
- Systematic issues including, regular late reporting of SAEs, 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).

Where such oversight committees are in use, cumulative safety information must also 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 TSC.

7.16 Reporting requirements for Trials of Devices

Medical devices used within the study should hold an appropriate conformity mark (UKCA or CE, as applicable under current UK legislation) and comply with the requirements for placement on the Great Britain market. Further information can be found in the MHRA's guidance on Regulating medical devices in the UK.

Be aware of appropriate naming when reporting events involving devices. These include ADEs, SADEs, and USADEs.

Where a clinical investigation of a device is being undertaken (pre-marketing), all adverse incidents involving non-CE or non-UKCA marked devices must be reported to the MHRA (Devices Division), whether initially considered to be device related or not. The legal responsibility for this lies with the manufacturer of the device. Further information can be found here: https://www.gov.uk/guidance/regulating-medical-devices-in-the-uk.

Device related SAEs involving CE and UKCA marked devices can be reported voluntarily by 'users' of the device. This could be a patient or healthcare professional but there is no regulatory requirement. In a trial which is using a CE or UKCA marked device, adverse events should be reported to the manufacturer.

7.17 SAE Reconciliation (WCTU)

This section describes the processes for SAE reconciliation within the WCTU. Similar processes should be followed for studies coordinated outside of the WCTU where human participants are involved and there is a requirement to monitor the safety profile of an intervention.

SAE reconciliation is a process used to confirm all reported SAEs have been consistently recorded and managed by both the study team and the WCTU QA team to protect participants and aid data integrity. The process involves comparing the SAE records maintained by the study team to identify any discrepancies, omissions, or inconsistencies and ensuring that these are resolved and appropriately documented.

An SAE reconciliation must be performed as a minimum following completion of study follow-up activities and before database lock and final analysis of study data.

Additional SAE reconciliations may be performed:

- At the request of the study team, the WCTU QA team, the sponsor, or oversight committees.
- Where concerns are identified relating to the completeness, accuracy, or consistency of SAE reporting.

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- Following significant protocol modifications which affect safety reporting requirements.

The reconciliation should be conducted jointly by representatives of the study team and the WCTU QA team.

The reconciliation process should involve comparison of all SAE records maintained by the study team with the SAE records maintained by the QA team. The purpose is to verify that:

- All reportable SAEs have been recorded by both teams.
- SAE reference numbers are correctly assigned and matched.
- No SAE reports are missing from either record set.
- Follow-up reports have been received, processed, and recorded consistently.
- All SAEs have come to a conclusion where they are resolved or unlikely to change.
- Any expedited reporting requirements have been met where applicable.
- The status of each SAE is accurately documented and aligned between records.

Any discrepancies identified during reconciliation should be investigated and resolved by the study team in consultation with the QA team.

Where reconciliation identifies missing SAE reports, inconsistencies in safety assessments, or evidence of non-compliance with reporting requirements, these should be escalated and managed in accordance with applicable WCTU procedures, including SOP 31 where appropriate. An audit trail of any corrections or amendments made as a result of the reconciliation should be retained within the TMF and any relevant study documentation.

The completion of each SAE reconciliation should be documented and retained within the TMF.

8 Templates

T51 – T57	SAE Template Forms

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