STANDARD OPERATING PROCEDURE 17
Safety

Part 2: Safety Reporting for Clinical Trials *other than* those of Investigational Medicinal Products

Version:	**4.0**	Effective Date:	13 Nov 2024
Issue Date:	30 Oct 2024	Review Date:	13 Nov 2026
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Revision Chronology:	Effective date:	Reason for change:
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	

STANDARD OPERATING PROCEDURE 17
Safety
Part 2: Safety Reporting for Clinical Trials *other than* those of Investigational Medicinal Products

1. Purpose and Scope

The purpose of part 2 of this Standard Operating Procedure (SOP) is to describe the process for safety reporting in research studies that do not involve an Investigation Medicinal Product (IMP). This applies to studies that are sponsored by the University of Warwick (UoW) or are externally sponsored and managed through Warwick Clinical Trials Unit (WCTU) and 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.

Details on the safety reporting requirements for Clinical Trials of Investigational Medicinal Products (CTIMPs) can be found in Part 1 of this SOP.

2. 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 adverse event 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.
Serious Adverse Event (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 of the study procedures.
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. For studies 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.

3. Background

The accurate and timely reporting of adverse events (AEs) in all clinical trials is a requirement of Good Clinical Practice (GCP). For CTIMPs, it is a legal requirement of the Medicines for Human Use (Clinical Trials) Regulations 2004 which enacts the EU Clinical Trials Directive. If your trial is covered by the Clinical Trials Directive, follow the directions given in Part 1 of this SOP 'Safety – Pharmacovigilance in CTIMPs'.

Clinical studies involving only CE marked medical devices, food supplements or other non-medicinal therapies (such as surgical or physiotherapy interventions) are not covered by these regulations, but still require that adverse events are managed according to 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/

4. Procedure

4.1 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 Research & Impact Services (R&IS) is responsible for safety reporting related to University of Warwick (UoW) sponsored studies. Where a research study is being managed by WCTU, this activity is delegated to WCTU and key oversight is maintained by the Sponsor's Office in R&IS. 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 for 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:

Chief Investigator (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 Trial Manager/Trial Coordinator (TM/TC) with the expectedness assessment of related SAEs • To submit reports to the Research Ethics Committee (REC) where there is a related and unexpected SAE. This task can be delegated to the TM/TC if appropriately documented. • Reporting of safety events to oversight committees • Regular monitoring of the risk benefit profile of the study
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 and causality assessment for any AEs.
Quality Assurance (QA) Team:	• Perform initial triage checks on incoming SAE. • Support the TM/TC to conduct expectedness assessment of related SAEs using 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 Sponsorship and Oversight Committee
Trial Manager/Trial Coordinator:	• To check SAEs according to the instructions in this SOP and liaise with investigator sites to obtain complete information about SAE reports received. • Conduct expectedness assessment in conjunction with the CI on related SAEs • Ensure systematic 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.
Senior Project Manager (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 University of Warwick Sponsorship and Oversight Committee in liaison with WCTU QA team.

4.2 When?

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

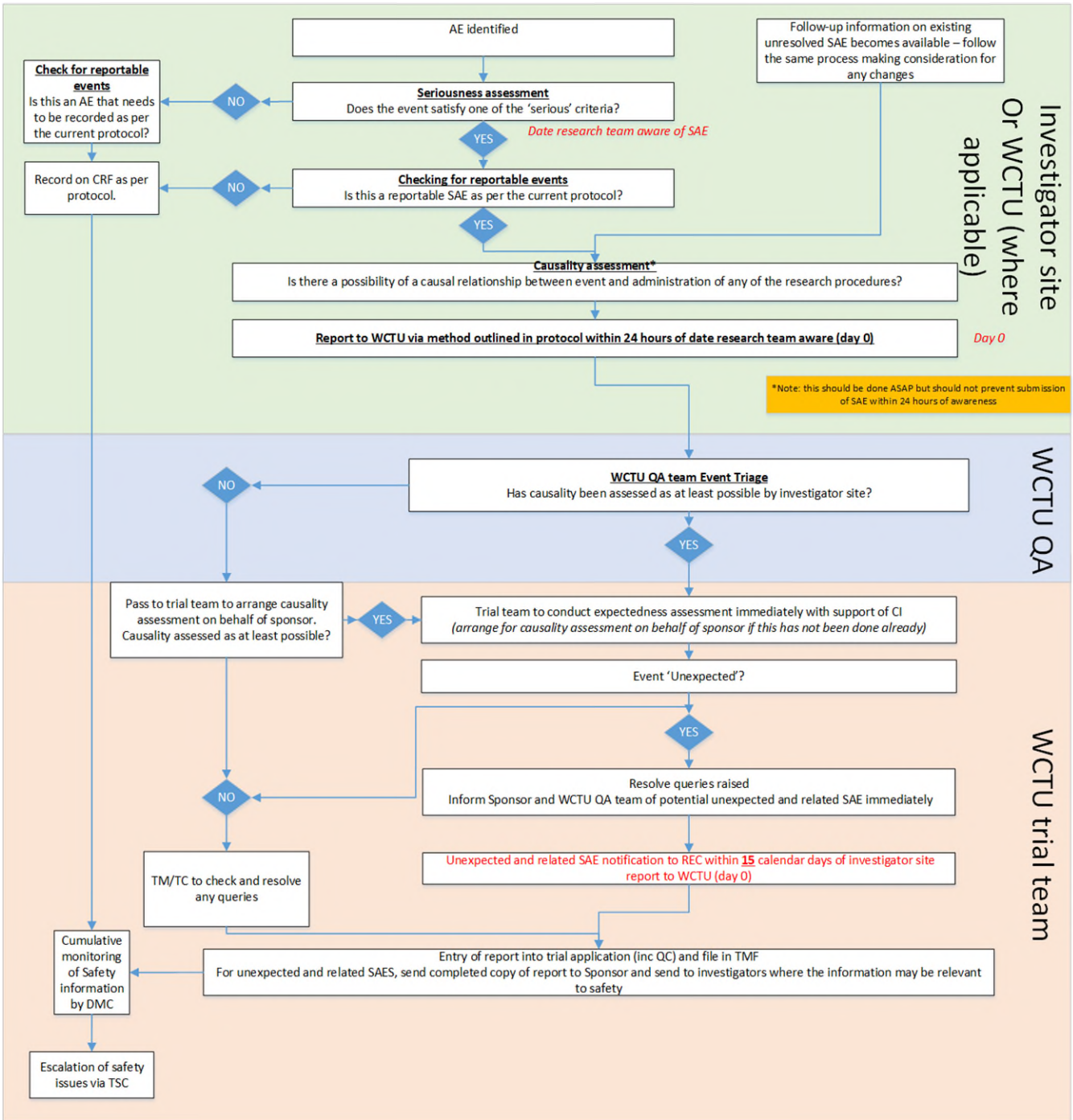
4.3 How?

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 Health Research Authority (HRA) and a 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.

Figure 2 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.



4.3.1 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 includes events from the time the participant gave informed consent until an appropriate time-point defined in the protocol.

- 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 AE form as this could lead to being counted twice in the analysis.

4.3.2 Identification of SAEs via other means

Potential SAEs may be identified by the coordinating centre rather than the investigator site via central monitoring activities such as data cleaning or during remote/on-site monitoring visits. There are situations where review of Participant Reported Outcome Measures (PROMs) / questionnaires (where they are submitted to the coordinating centre directly from the participant) 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 appropriate to ensure they are recorded in the CRF where required.

4.3.2.1 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 or delegate. 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 as noted at the monitoring visit.
- The investigator site should then perform tasks as outlined in this SOP.
- Failure to report an SAE to the sponsor via the mechanisms stated in the protocol is a violation of the protocol and GCP. This should be dealt with via the process outlined in SOP 31 Handling non-compliances, misconduct and serious breaches of GCP and/or study protocol'.

4.3.2.2 SAEs identified via PROMs submitted directly by participants

Where an SAE is identified via return of a participant outcome measure that does not go via an investigator site, the investigator site should be informed as soon as possible and asked to complete an SAE 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 can be completed by the coordinating centre themselves. There should be someone clinically or medically qualified to perform a causality assessment on 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.

Where an investigator site is a GP surgery or another primary care service, SAEs will usually need to be completed by the coordinating centre. 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 assessed in this way 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.

4.3.3 Seriousness assessment

An AE is considered 'serious' if it fulfils one 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.

4.3.4 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 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:

- Events for blinded studies which could unintentionally compromise the integrity of the blind
- SAEs which are serious but commonly experienced, e.g. anticipated events from disease progression.
- SAEs that form an outcome for the trial - 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.

4.3.5 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 Site Signature and Delegation log (SSDL).

Studies that are managed through WCTU should use the following five-point causality scale: 'definitely', 'probably', 'possibly', 'unlikely', 'unrelated'. Any SAE coded as definitely, probably, or possibly are considered to have a possible causal relationship.

An independent assessment of causality should also be done by the CI or clinical delegate on behalf of the sponsor (see section 4.3.10). This causality assessment is independent of the Investigator sites causality assessment.

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 will not suffice.

4.3.6 Reporting to the sponsor or WCTU

- SAEs should be reported to the sponsor or to the delegated person 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 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: 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 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 template which can be requested from the QA team.
- On receipt of the initial report, the report should be logged on the SAE database immediately by the WCTU QA Team triaged 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.

4.3.7 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 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 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 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 threating 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.

* *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 4.3.10 and 4.3.11 for more details.

4.3.8 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. 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 SAEs 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 study team 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 the sponsor (or the QA team where WCTU is managing the study) as soon as possible. Expectedness assessments are not required for events assessed to have no causal relationship (unlikely or unrelated).

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.

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 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 worst case scenario should be used to determine whether to expedite or not. Any differences in opinion should be provided in the expedited report. 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 can be someone else within the trial team or an independent person. The documentation of this delegation must be clear on a trial by trial basis. They 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.

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 administration of any of the research procedures. 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 QA team and 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 Sponsorship and Oversight Committee. Any concerns or queries raised will be directed back to the Trial Team.

4.3.12 Expedited reporting of unexpected and related SAEs

SAEs that have been assessed by the investigator as both having a possible causal relationship to the administration of the research procedures 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/

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.

It is important to keep detailed records of SAEs as they will form part of the annual progress reports submitted to the REC. Copies of all these reports and associated acknowledgements should be filed in the TMF.

4.3.13 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. 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. 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 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 steering committees.

If after unblinding the study intervention the participant has been allocated to a control group where no research procedures have been administered, then this will not usually satisfy the criteria for an unexpected and related event and therefore will not require expedited reporting. It is the CIs responsibility to report such cases at their discretion.

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 (SAEs and AEs) should be presented at Trial Management Group (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:

- 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).

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 Reporting requirements for Trials of Devices

To comply with UK legislation, manufacturers of devices must apply for their product to be UKCA marked before being placed on the UK market. This certifies that a product has met UK consumer safety, health or environmental requirements and is mandatory for many products on the market. Due to Brexit, from the 1st July 2023, CE marks will not be accepted for devices brought to the UK market.

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.

List of abbreviations

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
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigator Brochure
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
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
WCTU	Warwick Clinical Trials Unit