Standard Operating Procedure:

Adverse Event Reporting

# Purpose

This Standard Operating Procedure (SOP) describes the processes involved in Adverse Event (AE) reporting for clinical research projects conducted within the University of Birmingham (UoB).

# Scope

This SOP is applicable to all UoB sponsored clinical research. Where clinical research is sponsored by another institution, this procedure should be followed as far as possible, and in line with contractual agreements between the UoB and the other institution. This SOP also applies to clinical research approved by UoB Research Ethics Committee (REC) that are required to follow the UoB Principles of Good Clinical Practice (GCP) for Clinical Research (UoB-GCP-POL-001). This SOP may be used as a guidance document in all other cases.

# Implementation plan

This SOP will be implemented in line with this document’s effective date.

# Stakeholders

* Sponsor: for UoB sponsored clinical research projects this is via the Research Governance Team (RGT). Note that where the UoB takes on the Sponsor responsibility for AE reporting, the UoB will delegate the majority of these duties to the Chief Investigator (CI) and/or a Clinical Trials Unit (CTU), except where specified in this SOP. All delegation of duties will be documented (e.g. using CI declaration and/or the Clinical Trials Task Delegation Log (UoB-CLN-CTM-QCD-002)).
* CI: the CI may delegate activities to members of their research team, although evidence of CI involvement and approval is still expected and may not be delegated where ‘no delegation allowed’ is indicated. The SOP will state where delegation is possible. For clinical research approved by UoB REC, the role of CI may be referred to as the Principal Investigator (PI), or the supervisor for postgraduate research students.

# Background and rationale

The process of AE reporting is key to any clinical research, be it a Clinical Trial using an Investigational Medicinal Product (CTIMP), a Clinical Investigation of a Medical Devices, or another type of study. Furthermore, the need for, and responsibilities relating to, AE reporting are described as follows:

* For all UoB clinical research, see the [UoB Code of Practice for Research (PDF – 479 KB)](https://www.birmingham.ac.uk/Documents/university/legal/research.pdf).
* For all HRA-approved clinical research, see the [UK Policy Framework for Health and Social Care Research](https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/).
* For CTIMPs, [The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments](http://www.legislation.gov.uk/uksi/2004/1031/contents/made) detail the AE reporting requirements of the Sponsor or the Sponsor’s delegate.
* For medical devices being investigated in order to demonstrate the safety and performance of a non-CE marked medical device, or a CE-marked device that has been modified or is to be used for a new purpose the [Medical Devices Act 2002](http://www.legislation.gov.uk/uksi/2002/618/contents/made) detail the requirements for safety reporting. See also [Medical Device regulation and safety: detailed information](https://www.gov.uk/topic/medicines-medical-devices-blood/medical-devices-regulation-safety) and [Guidelines on Medical Devices (PDF – 384 KB)](https://ec.europa.eu/docsroom/documents/16477/attachments/1/translations/en/renditions/native).

For the purposes of this SOP the terms ‘clinical research’ or ‘research project’ will cover CTIMPs, other interventional trials (e.g. surgical trials, device trials and non-CTIMP trials, and any other projects deemed to be ‘interventional’ by the Sponsor), and clinical studies.

Where the requirement is specific to a certain type of clinical research, this will be specified in the instruction.

Clarification of terms

For the purposes of this SOP, the terms and definitions used are clarified as follows:

|  |  |  |  |
| --- | --- | --- | --- |
| Conditions | Clinical Research type | National Institute for Health Research (NIHR) term used | Term used in this SOP |
| If non-serious and not attributable to the research project: | All research projects | Adverse Event (AE) | Adverse Event (AE) |
| If non-serious but (possibly) attributable to the research project: | CTIMP and all clinical trials | Adverse Reaction |
| Medical Device | Adverse Device Effect (ADE) |
| Non-CTIMP | Related Event |
| If serious and not attributable to the research project: | All research projects | Serious Adverse Event (SAE) | Serious Adverse Event (SAE) |
| If possibly related to the research project and consistent with Reference Safety Information (RSI) (or equivalent): | CTIMP | Serious Adverse Reaction (SAR) | Serious Adverse Reaction (SAR) |
| Medical Device | Anticipated Serious Adverse Device Effect (ASADE) |
| If possibly related to the research project and **not** consistent with RSI (or equivalent): | CTIMP | Suspected Unexpected Serious Adverse Reaction (SUSAR) | Suspected Unexpected Serious Adverse Reaction (SUSAR) |
| Medical Device | Unanticipated Serious Adverse Device Effect (USADE) |

See Abbreviations and Definitions section at the end of the SOP for further terms used.

## Decision tree for AE reporting and timelines

# Process map



# Procedure

## Setup

### Decide on the level of AE reporting required

1. The CI (or delegate) will decide on the requirements for AE reporting in accordance with applicable regulations and guidance, based on the risk of the clinical research project to the participants and the research project objectives.
2. The CI (or delegate) will document the AE recording and reporting requirements (e.g., in the protocol or UoB REC application). See either Protocol Template - CTIMP (UoB-CLN-PRO-QCD-002) or Protocol Template - Non-CTIMP & Studies (UoB-CRT-NCTM-QCD-001). This will include:
* Decisions on which adverse events need to be recorded to ensure the safety of the participants and the integrity of the data.
* What AEs could reasonably be expected and the timeframe such events may appear.
* For studies, the CI (or delegate) will specify a process for recording and managing non-medical AEs; for example, distress caused by completing a psychological questionnaire may be managed by the inclusion of a helpline number at the end.
* For studies using a medicinal product according to its market authorisation, the AEs would be recorded, but where related to the treatment; reported through the normal method of yellow card scheme rather than through clinical research reporting routes.
* For trials, the CI (or delegate) will define any AEs that are of interest, or that are important to, the evaluation of the safety of the trial and document the reporting process.
* Decisions on the applicable product information; for CTIMPs it is the RSI and for other research projects it is the safety information provided; for the purposes of this SOP these are referred to as ‘RSI or equivalent’.
* That AEs and/or laboratory AEs/abnormalities identified in the protocol as critical to safety evaluations will be reported to the Sponsor according to the reporting requirements and within the time periods specified in the protocol.
* Ensuring the local regulations are adhered to when conducting a research project in a site based outside the UK.
1. The CI (or delegate) will decide whether certain Serious Adverse Events (SAEs) are expected, and list these in the protocol, detailing any expected SAEs that do not require expedited reporting, if applicable. Examples of SAEs may include:
* Pre-planned hospitalisation, e.g. for labour and birth, or pre-planned hip replacement.
* Prolongation of hospitalisation due to a wait for appropriate social care to be set up.
1. For CTIMPs, the CI (or delegate) will also specify in the protocol if there are any protocol-exempt SAEs or SARs that do not require reporting to the Sponsor. Protocol-exempt SAEs and SARs do not need to be included in the Development Safety Update Report (DSUR) line listing nor summary tabulations. Examples of protocol-exempt SAEs and SARs may include:
* Anticipated events from disease progression.
* Endpoints, e.g. death in myocardial infarction study.
1. For CTIMPs, the CI (or delegate) will ensure the RSI is identified or created to ensure it is known what AEs are expected for the IMP.
* The CI (or delegate) will prepare an Investigator Brochure (IB) if the IMP is being used outside its marketing authorisation. When creating the IB, the CI (or delegate) will refer to section 7 of the [ICH GCP E6 guidelines (PDF – 694 KB)](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf), which delineate the minimum information on what should be included in an IB and provides suggestions for its layout. See also the Essential Documents Development and Maintenance SOP (UoB-ESD-SOP-001).

### Develop processes for handling AEs and SAEs

1. The CI (or delegate) will develop forms and tools to capture AEs (and SAEs) for all research projects that includes the requirements for AE reporting (if applicable) according to the applicable regulations and/or guidance (see Safety Reporting and Timelines section below), ensuring that:
* Terminology for defining events and related terms on forms (e.g. severity and grade) aligns with that used in the database for reporting processes. See also the *Case Report Form Development SOP (UoB-CRT-CRF-SOP-001)* for further information.
* An SAE Form has been developed. See the *SAE Form template (UoB-AES-QCD-001)* for an example. For Medical Devices, it is expected that the [MEDDEV SAE template form](https://ec.europa.eu/docsroom/documents/16477/attachments/2/translations/en/renditions/pdf) is used.
1. For research projects where pregnancy may occur, the CI (or delegate) will develop a pregnancy notification form. See the *Pregnancy Notification Form (UoB-AES-QCD-003)* for an example.
2. If applicable, the CI (or delegate) will develop an internal process for SAE handling (see *Internal Process Example for SAE Handling (UoB-AES-QCD-002)*) and will ensure that any Sponsor specific requirements are embedded in the process.
* It is expected that an SAE tracking log is set up if more than 15 SAEs are anticipated.
1. For CTIMPs, the CI (or delegate) will establish and document a process for obtaining (alerts of) updates to the Summary of Product Characteristics (SmPC) or IB, as appropriate.
* Where the IMP is being supplied by the manufacturer, it is expected that it will be the responsibility of the IMP supplier (as outlined in a contractual agreement) to promptly notify the CI/CTU of any updates to the SmPC/IB.
* Where the above is not appropriate, the CI (or delegate) will develop a process to ensure checks for updated to the SmPC/IB are made and evidence at least every quarter.
1. For CTIMPs, the CI (or delegate) will ensure new user accounts are setup on the [Individual Case Safety Reports (ICSR) Submission portal](https://icsrsubmissions.mhra.gov.uk/login) for the reporting of SUSARs. For help with creating a new user account, please contact the RGT. See also [MHRA guidance](https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#report-an-urgent-safety-issue.) for further information on SUSARs and reporting to the MHRA.

Note: the eSUSAR website previously used for the submission of SUSAR reports to the MHRA was decommissioned at the end of September 2022 and only SUSARs via ICSR Submissions portal will be accepted from 01 October 2022.

### Training

1. The CI (or delegate) will ensure that site staff are appropriately trained on recording all AEs and the research project-specific AE reporting requirements and that training is documented (see Training SOP (UoB-TRN-SOP-001)). Training will include:
* That causality assessment decisions for medically related AEs will be made by a qualified doctor or, when appropriate, a qualified dentist; typically this is the PI. If the PI is not a qualified doctor (or dentist), this task will be formally delegated to a qualified doctor (or dentist) who is a member of the research team. The research project delegation log must reflect this delegation.
* That for Healthy Volunteer Studies the causality assessment will be made by the healthcare professional identified in the protocol to provide ongoing input into the study. See also Healthy Volunteer and Medical Oversight SOP (UoB-HVM-SOP-001).
* That when completing the causality assessment alternative causes, concomitant therapies, medical history and other risk factors will be considered, and that the assessment will be recorded and included in the medical notes, or source data where this is not the medical notes.
* That if a participant reports a SAE with a suspected causal relationship to the intervention after the treatment/involvement of the participant has ended (i.e. the participant is in follow-up), for the site to report the SAE to the CI (or delegate) without delay.
* A reminder of the possible need of reporting any SAEs to sites’ R&D departments as per local practices.
* Ensure that the CI (or delegate) is immediately informed of any SAEs (except for those identified in the protocol as not requiring immediate reporting), and when requested, to provide any further information.
* The need for sites to follow up on any AEs/SAEs until resolution or stabilisation.
* That for studies non-medical AEs may occur which do not need reporting but do need recording and managing in line with the protocol.
1. The CI (or delegate) will ensure that clinical staff reviewing SAEs on behalf of the Sponsor are appropriately trained on the project-specific AE reporting requirements, and that training is documented (see Training SOP (UoB-TRN-SOP-001)). Training will include:
* That clinical staff reviewing SAEs on behalf of the CI will be familiar with and use the latest version of the RSI or equivalent available at the time the event occurred.
* For clinical staff to review the causality assessment and determine the expectedness of the event, ensuring that this is documented, using clinical judgement by reviewing all documentation relating to the event.
* That for CTIMPs, detailed EU guidelines clearly state that the causality assessment should not be downgraded during this review. If the CI (or delegate) disagrees with the site’s initial causality assessment, the opinion of both parties should be documented, and where the event requires further reporting, the opinion should be provided with the report.
* That for Medical Devices clinical staff report to the CI (or delegate), without unjustified delay, all SAEs and device deficiencies that could have led to a Serious Adverse Device Effect (SADE) whether anticipated (ASADE) or unanticipated (USADE); this information will be promptly followed by detailed written reports.

## Monitor AEs throughout the research project

1. The CI (or delegate) will keep detailed records of all reported AEs relating to the research project, including those collected through the monitoring of data collection systems for AEs, and through e.g. monitoring of the research project; see *Data Management SOP (UoB-DMA-SOP-001)* and *Project Oversight and Quality Management SOP (UoB-POS-SOP-001)*, respectively.
2. For studies, the CI (or delegate) will also keep detailed records of all AEs (as detailed in the protocol) which have occurred but did not require reporting.
3. The CI (or delegate) will continuously weigh anticipated benefits and risks of the research project, which includes ongoing safety evaluation of the intervention. The CI (or delegate) will notify the RGT of any safety trends noted, in order that the RGT can pass the information on to researchers using the same intervention.
4. The CI (or delegate) will process any SAEs as per the pre-defined process. For the categorisation of SAEs:
* Review causality assessments, perform expectedness assessments, and refer to the RSI (or equivalent) in place at the time the event first occurred.
* For Health Research Authority (HRA) approved clinical research, the CI (or delegate) will refer to the appropriate online guidance to determine the correct categorisation of the event.
* For CTIMPs, follow the information on safety reporting in the [NIHR Clinical Trials Toolkit](http://www.ct-toolkit.ac.uk/routemap/safety-reporting/).
* For all other HRA approved clinical research, follow the information on the [HRA Safety Reporting website](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/).
* For UoB REC approved research, follow the [UoB Code of Practice for Research (PDF – 479 KB)](https://www.birmingham.ac.uk/Documents/university/legal/research.pdf).
* Note that where an increase in frequency or severity of an expected event occurs in an SAE this would then be classified as an Unexpected and Related SAE; for CTIMPs this is a SUSAR.
1. Where pregnancy occurs within a research project, the CI (or delegate) ensure the pregnancy is followed up and tracked to allow for collection of information on the pregnancy outcome.

## Safety reporting and timelines

1. The CI (or delegate) will be responsible for ensuring that AEs and SAEs are reported according to the stated timelines.
2. For CTIMPs, the CI (or delegate) will report all SUSARS within the following timeframes for:
* Fatal/life threatening SUSAR: initial report to the Competent Authority (CA), and REC within 7 days of being notified of the event, and any additional relevant information within 8 days of sending the first report. In the UK the CA is the MHRA, and ICSR submission portal is expected to be used for UK-relevant SUSARs, defined as either SUSARs originating in the UK, or SUSARs originating outside the UK where the Sponsor has an ongoing research project in the UK involving the same medicinal product. At the time the report is sent to the CA a copy will also be sent to the REC and RGT, including a note from the CI explaining how this case impacts the safety profile of the trial.
* Non-fatal/non-life threatening SUSAR: report to the CA and REC within 15 days of being notified of the event. A copy will also be sent at the time to the RGT including a note from the CI explaining how this case impacts the safety profile of the trial.
1. For CTIMPs which have sites in European member states, the CI (or delegate) will ensure all SUSARs have dual reporting via the ICSR Submissions portal and the relevant member states, as well as to the European database (Eudravigilance Clinical Trials Module ‘EVCTM’).
2. For CTIMPs, the CI (or delegate) will ensure that SAEs are reassessed on receipt of significant follow-up information using the RSI (or equivalent) approved at the time of the event:
* If significant new information is received following the reporting of an event (e.g. leading to upgrade or downgrade of category, duplicate events or reason for reporting) the reporting timeframe commences from receipt of the new information; this information will be reported to the REC, and CA where appropriate, with a copy sent to RGT as a follow-up report within 15 days. For CTIMPs, where a non-fatal/non-life threatening SUSAR is re-categorised (upgraded) as a fatal/life-threatening SUSAR, this will be reported within 7 days following the process described above.
* Other non-significant but relevant follow-up reports (e.g. resolution date) will be reported on resolution of the event.
1. For other HRA approved research projects (non-CTIMPs) including clinical investigations of a medical device, the CI (or delegate) will report only Unexpected and Related SAEs to the REC using the safety reporting form within 15 days of becoming aware of the event. A copy will also be sent at the time to RGT including a note from the CI explaining how this case impacts the safety profile of the study. See [HRA Procedures for Safety Reporting](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/) for more information.

### Medical device safety reporting

1. The CI (or delegate) will document details of the following reportable events during the research project:
* Any SAE.
* Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
* Any new findings in relation to any event referred to in points above.
1. The CI (or delegate) will document and assess all device deficiencies throughout the research project. See BS EN ISO 14155:2020, Clinical investigation of medical devices for human subjects — Good clinical practice for further information (see reference details below).
2. The CI (or delegate) will report the events mentioned in point 23 to the Sponsor immediately but not later than 3 calendar days after research project personnel’s awareness of the event and:
* Include a note from the CI explaining how this case impacts the safety profile of the research project.
* Report all relevant safety information to the Data Monitoring Committee (DMC).
1. The CI (or delegate) will assess the relationship between the use of the medical device (including the medical surgical procedure) and the occurrence of each AE categorised.
* During causality assessment activity, clinical judgement will be used and the relevant documents, such as the IB, the Clinical Investigation Plan or the Risk Analysis Report will be consulted, as all the foreseeable SAEs and the potential risks are listed and assessed there.
* The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors will be considered. The above considerations apply also to the SAEs occurring in the comparison group.
* For the purpose of harmonising reports, each SAE will be classified according to 5 different levels of causality. The following assess the relationship of the SAE to the investigational medical device or procedures.
* 1) Not related - relationship to the device or procedures can be excluded.
* 2) Unlikely - the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
* 3) Possible - the relationship with the use of the investigational device is weak but cannot be ruled out completely.
* 4) Probable - the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
* 5) Casual Relationship - the serious event is associated with the investigational device or with procedures beyond reasonable doubt.
* Where it remains uncertain about classifying the SAE, it will be classified as “possible”. See [EU guidelines](https://ec.europa.eu/docsroom/documents/16477/attachments/1/translations/en/renditions/native) for further details.
1. The CI (or delegate) will report to the CA in which the research project is being conducted:
* All reportable events described in point 23 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/participants, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by Sponsor of a new reportable event or of new information in relation with an already reported event.
* Any other reportable events as described in point 23 or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the Sponsor of the new reportable event or of new information in relation with an already reported event.

## Urgent safety measures

1. The CI (or delegate) will ensure that where urgent safety measures are taken in order to protect the health and safety of participants of any research project against any immediate hazard, the REC, RGT and where applicable the CA will be notified immediately by telephone. The CI (or delegate) will ensure any urgent safety measures are then confirmed in writing within 3 working days that such measures have been taken, the reasons why and the plan for further action. See [MHRA guidance on urgent safety measures](https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#urgent-safety-measures) for further details.
2. Copies of the information will be provided to the REC that approved the research project using the appropriate REC safety reportingcover sheet (see [HRA urgent safety measures (all studies)](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/) for more information).
3. The CI (or delegate) will ensure that participants are given the option to re-consent or to withdraw from the research project if urgent safety measures are implemented to protect the participant against any immediate hazard to their health safety.

## Communicating safety issues

1. The CI (or delegate) will inform the Sponsor (RGT) of any potential significant safety issues that may have to be reported to any other research projects in the Sponsor’s portfolio using the same IMP/medicine/intervention.
2. The CI (or delegate) will inform relevant third parties (where this is a contractual requirement) of any relevant safety data or significant safety issues as appropriate (this does not include sites).
3. Upon receipt of safety information, the RGT (as the Sponsor) will ensure CIs of any other research projects in the Sponsor’s portfolio using the same IMP/medicine/intervention are updated within 10 working days of any potentially significant safety issues. The RGT will also assess the impact upon sponsorship/insurance or contractual obligations and respond as necessary, and where applicable, will ensure all relevant research projects are updated in the event of the supplier issuing a revised SmPC.
4. The CI (or delegate) will:
* Inform site staff of any safety issues in a timely fashion; for CTIMPs this includes forwarding information about SUSARs.
* Where a DMC is in place, ensure safety information is made available for the DMC review at the scheduled time points.
* Ensure urgent DMC to convene where appropriate and make assessment on all safety information. DMC to advise CI of the decisions.

## Annual reporting and validation

1. The CI (or delegate) will ensure annual reporting is undertaken as required and that all relevant documentation including acknowledgment receipts are filed in the Study/Trial Master File (S/TMF):
* For CTIMPs, a DSUR is completed and sent to the CA and REC on an annual basis with a copy to RGT (Sponsor); see *DSUR template (UoB-CLN-AES-QCD-004)* for an example. See also [MHRA guidance on DSUR Submissions](https://www.gov.uk/guidance/guidance-on-submitting-clinical-trial-safety-reports#submitting-development-safety-update-reports-dsurs-to-the-mhra).
* The date the DSUR is due is the anniversary of the first Clinical Trial Authorisation (CTA), for research projects with marketed products the date is the first marketing authorisation granted in the EU.
* For all HRA-approved research projects, safety information is included in the Annual Progress Report and sent to the REC with a copy to RGT on an annual basis. See also [HRA guidance on Progress Reports](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/).
* For clinical investigations of medical devices, within 30 days following the anniversary of the authorisation date for the clinical investigation the CI (or delegate) will report details of all SADEs (including USADEs) in the Annual Safety Report to the MHRA and main REC. A copy of the report will also be sent to the Sponsor and the manufacturer.
1. For CTIMPs, the CI will review and approve the DSUR prior to submission. Where it is not felt appropriate for the CI to review the DSUR, another independent clinician should be appointed to assume this role.
2. For CTIMPs, the CI (or delegate) will ensure the IB (where the CI is responsible for the IB) is reviewed at least once a year and confirm to the RGT that this has occurred. Where an existing IB or SmPCs is used, the CI (or delegate) will ensure the content of an existing IB or SmPCs (if multiple are used) and urgent safety reports are (the source for) the RSI, is reviewed at regular intervals as defined in the trial specific risk assessment, and as a minimum prior to submitting the annual DSUR and confirm to the RGT that this has occurred, at the time of the DSUR submission.
* Where the RSI has changed:
* Submit a substantial amendment to the CA at the same time as submitting the DSUR. The amendment should reference and be supported by the DSUR. Note: the revised RSI can only be implemented once approval from the CA has been received.
* Attach old and revised RSI as Appendix 1 of the DSUR.
* Where the RSI has not changed, attach the (unchanged) current RSI to the DSUR.

## At the end of the research project

1. The CI (or delegate) will ensure all reported AEs and SAEs are archived:
* If SAE information is kept in a separate system, ensure information is reconciled with the main research project database.
* Ensure SAE forms and related information are archived as part of the S/TMF.

# List of expected outputs

* A section in protocol regarding all AE reporting requirements and, if applicable, listing expected SAEs and detailing SAEs that do not require expedited reporting.
* An SAE reporting form.
* For clinical investigations of medical devices: A Device Deficiency reporting form.
* Evidence of delegation for AE reporting procedures to site and causality assessments.
* Evidence of training of research project staff on AE reporting procedures.
* A repository for capturing individual safety reports including AEs.
* For clinical investigations of medical devices: A repository for capturing individual Device Deficiency reporting forms.
* An SAE tracking log, if more than 15 SAEs be expected.
* Evidence of causality of SAEs conducted by a qualified medical professional, where applicable.
* Evidence of SAEs reported to Sponsor, as required (and for Medical Devices, to the MHRA and manufacturer) and follow-up information.
* For CTIMPs: Evidence of SUSARs reported to CA and REC on time, with a copy sent to RGT.
* For CTIMPs: DSURs submitted to the CA and REC on time, with a copy sent to RGT.
* For CTIMPs: Evidence of IB/SmPC being validated annually and reported to RGT.
* For all HRA approved research projects: Annual Progress Report(s) submitted to the REC on time, with a copy sent to RGT.
* For clinical investigations of medical devices: Evidence of (U)SADEs reported to CA and REC on time, with a copy sent to the Sponsor/RGT.
* For clinical investigations of medical devices: Evidence of an Annual Safety Report being sent by the CI (or delegate) to the CA and REC on time, with a copy sent to RGT.
* Documented evidence of the identification, management and resolution of any major safety issues.
* For externally sponsored research projects: Evidence of delegation of these duties detailed above, including within the contractual agreement, and evidence of adherence to those processes.

# Related documents

* UoB-AES-QCD-001 SAE Form template
* UoB-AES-QCD-002 Internal process for SAE handling example
* UoB-AES-QCD-003 Pregnancy Notification Form
* UoB-CLN-AES-QCD-004 DSUR template
* UoB-CLN-PRO-QCD-002 Protocol template – CTIMPs
* UoB-CRT-CRF-SOP-001 Case Report Form Development
* UoB-CRT-NCTM-QCD-001 Protocol template – Non-CTIMPs and Studies
* UoB-DMA-SOP-001 Data Management
* UoB-ESD-SOP-001 Essential Documents Development and Maintenance
* UoB-GCP-POL-001 UoB Principles of GCP for Clinical Research
* UoB-HVM-SOP-001 Healthy Volunteers and Medical Oversight
* UoB-POS-SOP-001 Project Oversight and Quality Management
* UoB-SPO-QCD-001 Clinical Trial Task Delegation Log
* UoB-SPO-SOP-001 Sponsor Oversight of Clinical Research
* UoB-TRN-SOP-001 Training

Note the UoB QMS documents can be found on the [CRCT website](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/index.aspx). Internal work instructions can be obtained from the CRCT (crct@contacts.bham.ac.uk) and/or from the RGT (researchgovernance@contacts.bham.ac.uk).

# References and frameworks:

* British Standards Institution, BS EN ISO 14155:2020 - Clinical investigation of medical devices for human subjects — Good clinical practice, ISBN 978 0 580 94915 9. Can be accessed via: [https://bsol.bsigroup.com](https://bsol.bsigroup.com/) (requires UoB login).
* European Guidelines on Medical Devices: <https://ec.europa.eu/docsroom/documents/16477/attachments/1/translations/en/renditions/native>
* European Medical Device Regulation 2017/745: <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0745&from=EN>
* HRA Progress Reports and Safety Reporting: [https://www.hra.nhs.uk/approvals-amendments/managing-your-approval](https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/)
* ICH Guidelines on scope and content of a Development Safety Update Report (DSUR): <https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-26.pdf>
* ICH GCP: <https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf>
* ICSR Submission portal: <https://icsrsubmissions.mhra.gov.uk/login>
* MEDDEV SAE Form Template: <https://ec.europa.eu/docsroom/documents/16477/attachments/2/translations/en/renditions/pdf>
* Medical Devices Act 2002: <http://www.legislation.gov.uk/uksi/2002/618/contents/made>
* Medical Devices safety requirements: <https://www.gov.uk/topic/medicines-medical-devices-blood/medical-devices-regulation-safety>
* MHRA guidance and requirements for safety reporting: <https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues>
* MRC/DH/MHRA “Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products” <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf>
* NIHR Clinical Trials Toolkit - Guidance on safety reporting: <http://www.ct-toolkit.ac.uk/routemap/safety-reporting/>
* Regulation (EC) No 1394/2007 of the European Parliament and of the council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004’: <https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing>
* The Medicines for Human Use (Clinical Trials) Regulations 2004, part 5, EU 2011/C 172/01: ‘CT-3’, June 2011: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use’ (subsequently referred to as the detailed guidance): <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2011:172:0001:0013:EN:PDF>
* The Medicines for Human Use (Clinical Trials) Regulations 2004: <http://www.legislation.gov.uk/uksi/2004/1031/contents/made>
* UK Policy Framework for Health and Social Care Research: <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/>
* UoB Code of Practice for Research: <https://www.birmingham.ac.uk/Documents/university/legal/research.pdf>

# Abbreviations and definitions

| Term | Description |
| --- | --- |
| Adverse Device Effect (ADE) | Adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device. |
| Adverse Event (AE) | Any untoward medical occurrence in a participant or clinical research participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.Comment: An Adverse Event can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.For studies and trials sponsored by UoB it is an event, which results in or may result in harm or damage to the interests the Researcher, the research participants, the University (including its reputation), society, the environment or a failure to maintain appropriate standards of animal welfare. |
| Adverse Reaction (AR) | For CTIMPs, all untoward and unintended responses to an investigational medicinal product related to any dose administered. |
| **Competent Authority**(CA) | A body with authority to act on behalf of the government of the EU Member State to perform a designated function; in the case of clinical trials, to ensure that requirements of the Clinical Trials Directive are transposed into national law and applied. The Medicines and Healthcare products Regulatory Agency (MHRA) is the ‘competent authority’ UK. |
| Device Deficiency | Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer. |
| Healthcare professional | A healthcare professional is defined as an authorised healthcare professional, or a qualified and registered (or alike) [Allied Health Profession](https://www.england.nhs.uk/ahp/role/) such as a physiotherapist, dietitian or radiographer. |
| Reference Safety Information (RSI) | Term used within EC Detailed Guidance (CT3) June 2011, meaning the applicable product information which is used to determine the expectedness of an Adverse Reaction. This information is normally obtained from within the Summary of Product Characteristics or Investigator Brochure; when referring to the Investigator Brochure the relevant section must be defined. It may be a separate document in its own right. It must be defined at the start of a trial.  |
| Serious Adverse Device Effect (SADE) | Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| Serious Adverse Event (SAE) | Any untoward medical occurrence or effect that at any dose: * Results in death
* Is life‑threatening\*
* Requires hospitalisation or prolongation of existing inpatients’ hospitalisation
* Results in persistent or significant disability or incapacity
* Is a congenital anomaly/birth defect
* Or is otherwise considered medically significant by the Investigator\*\*

Comments: The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria.\* Life threatening in the definition of an 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 that hypothetically might have caused death if it were more severe.\*\* Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious. |
| Serious Adverse Reaction (SAR) | For CTIMPs, an adverse reaction which also meets the definition of a Serious Adverse Event. |
| Summary of Product Characteristics (SmPC) | Summary of product characteristics (SmPC) describes the properties and conditions for use of a particular medicinal product, and is the basis of information for health professionals on how to use the medicinal product safely and effectively. It includes the composition, pharmaceutical form and strength, approved indications, side effects, warnings and precautions for use, shelf life, storage conditions and the name of the marketing authorisation holder. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | For CTIMPs, a Serious Adverse Reaction that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an Adverse Reaction, an Unexpected Adverse Reaction and a Serious Adverse Reaction. |
| Unanticipated Serious Adverse Device Effect (USADE) | Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Note: Anticipated SADE (ASADE) is an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report. |
| Unexpected Adverse Reaction (UAR) | For CTIMPs, an Adverse Reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product). |
| Unexpected and Related Event | For non-CTIMPs, an event which meets the definition of both an Unexpected Event and a Related Event. |
| Unexpected Event | For non-CTIMPs, the type of event that is not listed in the protocol as an expected occurrence. |

See also the [Glossary of Terms](https://www.birmingham.ac.uk/research/activity/mds/mds-rkto/governance/Glossary-of-Terms.aspx).