Standard Operating Procedure for the Recording, Management and Reporting of Adverse Events by Investigators

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Revision Chronology:			
SOP ID Number:	**Effective Date:**	**Reason for Change:**	**Author:**
CRN/04/S05/00	09/09/2004	N/A	Yvanne Enever
BRD/04/S05/01	20/04/2005	Administrative changes i.e. email address update. UCL CRN to UCL Biomedicine R&D Unit. Removal of UCL SAE Follow-up Form. Update of UCL SAE Reporting Form.	Yvanne Enever
BRD/04/S05/02	25/10/2005	Administrative changes i.e. UCL logo. Additional text P2 to clarify version number, plus addition of CI expectedness evaluation, changes in staff titles.	Yvanne Enever
JBRU/07/S07/00	18/06/2007	Implementation of the Joint UCL/UCLH Biomedical Research Unit, clarification of definitions, inclusion of pregnancy, unblinding, update SAE report form, overdose reporting and a new numbering system.	Farhat Gilani
JBRU/07/S07/01	20/12/2007	Update SOP in response to MHRA Inspection to ensure all AE/Rs are recorded and reported accordingly. In particular procedure for pregnancy reporting has been updated.	Farhat Gilani
JBRU/INV/S05/02	28/10/2008	To make SOP specific to investigator responsibilities and clarify reports on deaths. To implement a new JBRU numbering system as reflected in SOP on SOPs JBRU/INT/S01/02	Joanna Galea-Lauri
JBRU/INV/S05/03	10/01/2010	To amend the SAE form and provide alternatives in the absence of the Senior Pharmacovigilance Co. format amended in line with revised SOP on SOPs to incorporate a UCL logo only, an Acronyms table, eDocument file path, associated templates/log table, SOP dissemination and training and a signature page.	Anne Marie Downey
JRO/INV/S05/04	11/01/2012	Update SOP to reflect current system including e-SUSAR reporting, SPC review, DSUR, Drug Alerts and Safety Warnings, Safety Management Plan, Overdose and Sponsor Oversight.	Farhat Gilani
JRO/INV/S05/05	16/06/2012	Administration update and removal of forms from SOP.	Farhat Gilani
JRO/INV/S05/06	12/12/2013	Formatting and administration changes	Farhat Gilani
JRO/INV/S05/07	30/10/2016	Minor clarifications only	Farhat Gilani
JRO/INV/S05/08	22/12/2019	Updates to definitions, additional information regarding management of RSI and expectedness assessments, procedures for blinded trials, updated workflow diagram, formatting and minor clarifications	Catherine Maidens
JRO/INV/S05/09	06/01/2023	Minor clarifications, updates to safety reporting requirements to REC, added timelines for SUSAR reporting, details on periodic AE reviews.	Catherine Maidens

ACRONYMS:	
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial Investigational Medicinal Product
CTR	Clinical Trials Regulation
DMC	Data Monitoring Committee
DSMC	Data Safety Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JRO	Joint Research Office www.ucl.ac.uk/joint-research-office
PI	Principal Investigator
PV	Pharmacovigilance
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SI	Statutory Instrument
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
SUSAR	Serious Unexpected Suspected Adverse Reaction
TMF	Trial Master File

Contents

Standard Operating Procedure for the Recording, Management and Reporting of Adverse Events by Investigators

1. PURPOSE

This Standard Operating Procedure (SOP) has been written to describe the procedure to be followed by the Investigator for the recording, management and reporting of Adverse Events (AEs) which occur in trial participants in Clinical Trials of Investigational Medicinal Products (CTIMPs). It will further describe the procedure for periodic review of AEs, Reference Safety Information (RSI) document updates, management of pregnancy, overdose reports and safety alerts.

2. JOINT RESEARCH OFFICE POLICY

All SOPs produced from the JRO must be used in conjunction with local NHS Trust and UCL policies and procedures.

The JRO acts as the representative of the Sponsor and will be the official name used on all SOPs.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in Directives 2001/20/EC and 2005/28/EC (in the UK, these Directives were transposed into UK law by SI 2004/1031, SI 2006/1928) and subsequent amendments. Where applicable it incorporates elements of ICH GCP tripartite guidelines (E6).

In addition, as UCL sponsors trials with EU and Northern Ireland sites, the SOPs are written to comply with EU Clinical Trials Regulation No. 536/2014 (CTR).

For further guidance refer to:

European Commission's Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'), 2011

Clinical Trial Facilitation Group (CTFG) guidance - Q&A Document: Reference Safety Information, Nov 2017.

Clinical Trials Facilitation and Coordination Group (CTFG) Recommendations related to contraception and pregnancy testing in clinical trials, V1.1, 21/09/2020

For convenience, this document will use the term "UK Regulations" to cover the UK legislation and the EU Clinical Trials Directive.

To comply with the UK Regulations which set out the responsibilities of the sponsor and investigator, this SOP will focus on the trial site team procedures for the adequate recording, evaluation and reporting of Adverse Events in trials involving Investigational Medicinal Products (IMPs). It will further outline the Investigator's responsibilities to ensure oversight and management of pharmacovigilance systems in UCL sponsored trials.

3.1 Definitions

The following definitions have been adapted from the UK regulations:

Adverse Event (AE)

Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

Therefore an AE can be any unfavourable or unintended change in the structure (signs), function (symptoms) or chemistry (laboratory data) in a subject to whom an IMP has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

This definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

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

Any adverse event or adverse reaction in a trial subject that:

(a) **requires hospitalisation or prolongation of existing hospitalisation**;

Note: hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Therefore, participants do not need to be hospitalised overnight to meet the hospitalisation criteria. Hospitalisation (including hospitalisation for an elective procedure) for a pre-existing condition (prior to study entry) which has not worsened does not constitute a serious experience

(b) **results in persistent or significant disability or incapacity**;

Note: substantial disruption of one's ability to conduct normal life functions

(c) **results in a congenital anomaly or birth defect**;

Note: in offspring of subjects or their partners taking the IMP regardless of time of diagnosis

(d) **is life threatening; or**

Note: places the subject, in the view of the investigator, at immediate risk of death from the experience as it occurred, this does not include an adverse experience that, had it occurred in a more severe form, might have caused death

(e) **results in death**

Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such **important medical events** should also be considered as serious.

*The term "**severe**" is often used to describe the intensity of an event or reaction (e.g. mild, moderate or severe) and should not be confused or interchanged with the term "**serious**".*

Suspected Unexpected Serious Adverse Reaction (SUSAR)
A serious adverse reaction, the nature, severity or outcome of which is not consistent with the Reference Safety Information.

Reference Safety Information (RSI)
A list of medical events that defines which reactions are expected for the IMP being administered to clinical trial subjects, and so do not require expedited reporting to the Competent Authority. It is contained in a specific section in the Summary of Product Characteristics (SmPC) or the Investigator's Brochure (IB).

3.2 Key Responsibilities for the Investigator

This section describes the key pharmacovigilance responsibilities of the Investigator, further delegation of these responsibilities to other team members must be documented on the Trial Delegation of Responsibilities Log.

1	**Adverse Event Recording:** The Investigator must ensure all Adverse events (AEs) are assessed, recorded and reported to the JRO as defined in the trial protocol and this SOP.
2	**Pregnancy Monitoring:** The investigator must monitor and report pregnancies to the JRO if specified in the protocol.
3	**Periodic Review of Adverse Events:** The Investigator must periodically review and analyse trial safety information to identify and mitigate any risks associated with the trial interventions and to assess the ongoing risk-benefit of the trial.
4	**Development Safety Update Report (DSUR):** In conjunction with the JRO, the CI must aid in the production of the DSUR.
5	**Reference Safety Information:** Any updates to the Reference Safety Information (RSI) document (Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC)) must be reviewed by the Chief Investigator (CI) to confirm if the new information impacts the trial and participant safety and if any amendments are required to the trial documents. An updated RSI document must be submitted to the MHRA as a substantial amendment if there is a change to the RSI (new events listed or removed) or other changes likely to have an impact on the safety of the trial participants or conduct of the trial, or if they are otherwise significant. The new version cannot be used as RSI until it is approved.
6	**Overdose Reports:** The Investigator must inform the JRO of all overdoses. In the event that the overdose is associated with an adverse event, an SAE Reporting Form must be completed and forwarded to the JRO.
7	**Other Safety Issues:** Safety issues, which might materially alter the current benefit-risk assessment of the trial but which do not meet the definition of a SUSAR, may occur during a trial. The investigator must inform the JRO immediately should they become aware of any such safety issues.
8	**Safety warning and drug alerts:** These must be reviewed by the CI to assess whether any actions are required to protect participant safety. The information must be forwarded to the JRO with any recommendations and what actions (if any) are required.

4. SCOPE OF THIS SOP

What this SOP covers

This SOP covers the procedures for the recording, management and reporting of all Adverse Events (AEs) that occur in trial participants in CTIMPs sponsored by UCL. It will further describe the procedure for periodic review of AEs, Reference Safety Information (RSI) document updates, management of pregnancy, overdose reports and safety alerts.

What this SOP doesn't cover

In circumstances where the JRO (in its role as Sponsor or a legal representative of the Sponsor) has delegated the responsibilities to a third party such as a Clinical Research Organization (CRO) or an external Clinical Trials Unit (CTU), the pharmacovigilance procedures will be outlined in a trial specific agreement between the Sponsor, the CRO and the Chief Investigator, and applicable third party SOPs. Therefore description of this procedure falls outside the scope of this SOP.

5. RESPONSIBLE PERSONNEL

The Investigator is responsible for keeping records of all adverse events that occur in trial participants at their site as per the trial protocol.

The Investigator may further delegate who within the trial team is responsible for assessing causality of AEs and reporting Serious Adverse Events (SAEs) to the Sponsor. Delegated individuals must be qualified to perform the delegated task, and authorised in the Delegation of Responsibilities Log.

6. PROCEDURE

6.1 Investigator Procedure for Adverse Event Recording, Assessment and Reporting

6.1.1 Recording Adverse Events

The table below provides guidelines for where to record **Adverse Event** information, also refer to the protocol:

Type of Adverse Events	**Format of Recording Information**
All **Adverse Events** ***(including SAEs)***	Medical Records, AE section of CRF / trial database
SAEs	Trial Specific SAE Reporting Form

- **All adverse events** must be recorded and reported within the time period clearly defined in the trial protocol.
- All event terms should be a **diagnosis**, where possible, as opposed to signs and symptoms. Event terms should not be recorded as procedures, but rather the medical reason for the procedure.
- The following events do not require recording in the CRF / SAE Reporting Form, however they should still be recorded in the participants medical notes.

  Hospitalisation for:

  - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - Any admission to hospital or other institution for general care where there was no deterioration in condition.
  - Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.
- In addition, the protocol may specify other adverse events that do not need recording or reporting to Sponsor (e.g. anticipated disease related symptoms, common side effects of the IMP).

6.1.2 Evaluation of Adverse Events

The following documents need to be referred to when assessing any adverse event in the trial:

- Protocol
- Safety Reference Document (Summary of Product Characteristics (SmPC), Investigator's Brochure (IB)

Each adverse event must be evaluated for **causality**, **severity** and **seriousness**. The Investigator should make these assessments which are documented on the CRF / SAE Reporting Form.

Please also refer to the **Adverse Event Decision Flowchart** in **Appendix 1**.

Assessment of Causality:

- The assessment of whether there is a **reasonable possibility of a causal relationship** is made by the Investigator. Every effort must be made by the Investigator to obtain all the required information to determine whether the adverse event is related to the trial intervention.
- The Investigator should consider the following before reaching a decision:
    - Temporal relationship (time of onset and time of IMP administration)
    - Information about the drug (e.g. commonly occurring Adverse Drug Reactions)
    - Medical History and concurrent illnesses
    - Lack of efficacy/worsening of existing condition
    - Other medications (concomitant, non-IMPs)
    - Other trial procedures
    - Withdrawal of study treatment
    - Erroneous treatment with study medication (or concomitant / non-IMP)
    - Drug interactions
- It is important to note that if the Investigator indicates an unknown causality assessment for an SAE the event will be considered as related by the JRO (taking the most conservative option) and could warrant expedited reporting.
- For multi-site trials the CI cannot downgrade a PI's causality assessment of an event but the CI may upgrade an event.

Assessment of Severity:

- Adverse events should be assessed for clinical severity (intensity defined as: **mild, moderate or severe**, or **grades 1-5**) of the specific event.
- The severity grading to be used and any reference documents such as Common Terminology Criteria for Adverse Events (**CTCAE**) will be documented in the protocol.
- Severity must not be confused with "serious" which is a regulatory definition based on event outcome or action criteria.

Serious Criteria Assessment:

- The investigator must assess whether the adverse event meets one of the **serious criteria** as per the definition of an SAE in Section 3.1.
- The **onset date** of an SAE should be recorded as the **date the event met a serious criterion** (e.g. date of hospital admission).
- The **resolution date** of an SAE should be recorded as **the date the event no longer met a serious criterion** (e.g. where hospitalisation is the only serious criterion this would be the date of hospital discharge).
- Where symptoms started before a participant was hospitalised, or continued after discharge, additional non-serious adverse events should be added to the CRF as appropriate.

6.1.3 Reporting SAEs to the JRO

- Report all adverse events that fulfil the criteria for the definition of **serious** (*refer to Section 3.1*) to the JRO on a trial specific **SAE Reporting Form as soon as possible and no later than 24 hours** after site awareness, unless specified in the protocol.

SAE Reporting Form must be emailed to the JRO at **sae@ucl.ac.uk**

- The Investigator (or delegated medically qualified person making the causality assessment) must **sign and date** where indicated on the SAE Reporting Form. The completed report should be printed, signed and scanned, or an electronic signature added to a pdf file of the report, using Adobe or DocuSign.
- **Participant confidentiality** and adherence to the Data Protection Act (2018) must be maintained in relation to recording and reporting of adverse events. No personal identifiable data (including name, initials, date of birth, hospital number) must be forwarded to the JRO or other external organisations.
- The reporter will receive an **acknowledgment** of the report from the JRO. In the event that the SAE is not acknowledged **within 3 working days**, the site should contact the JRO to confirm receipt of the report.
- The Investigator must respond promptly to any **queries** raised by the JRO.
- The protocol may list certain **Adverse Events of Special Interest (AESIs),** which although may not meet a serious criterion should still be reported to the JRO in the same manner as an SAE.
- All SAE reports and associated correspondence should be **filed in the Investigator Site File** (ISF).
- All SAEs must be added to the CRF / trial database in a timely manner. A listing of AEs/SAEs recorded on the trial should be sent to the JRO for review upon request for the purposes of **SAE reconciliation** between the **trial database** and the **JRO safety Database**.

6.1.4 Follow-up Reports

- All SAEs should be followed up until a **resolution** is reached (i.e. recovered, recovered with sequelae, or fatal).
- On receipt of relevant updates for the SAE, site staff must send a follow-up report to the JRO as per section 6.1.3, **as soon as possible and no later than 24 hours** after the site was made aware of the updated information.
- If only minor updates are needed the initial SAE report can be amended, ensuring all updates are initialled and dated, or if completing the form electronically use tracked changes in MS Word. Ensure the 'type of report' box is updated to 'follow-up' with the follow-up report number added, and the report is resigned and dated by the Investigator.
- If major updates are needed complete a new SAE Reporting Form.

6.1.5 Assessment of Expectedness by Sponsor

- For SAEs that are considered related to the IMP (**Serious Adverse Reactions - SARs**) an expectedness assessment will be performed by the JRO Pharmacovigilance Manager (or in their absence another member of the JRO team).

- The SAR will be evaluated to assess whether it is '**expected'** or '**unexpected'** against the current approved **Reference Safety Information (RSI)** for the trial (i.e. a specific section in an IB or SmPC).
- If an SAR is assessed as unexpected it meets the criteria of a **Suspected Unexpected Serious Adverse Reaction (SUSAR)** and will be subject to expedited reporting by the JRO to the MHRA and REC (*where applicable*) within the following timelines:
    - **Fatal** or **life threatening SUSARs** must be reported as soon as possible, but no later than **7 calendar days** after the JRO is made aware of the reaction. If the initial report is incomplete any additional relevant information must be sent within an additional 8 calendar days of the initial report.
    - **Non-fatal** or **non-life threatening SUSARs** must be reported as soon as possible but no later than **15 calendar days** after the JRO is made aware of the reaction.
- For multi-site trials the CI will be requested to disseminate the SUSAR report to all trial PIs.

6.2 Investigator Procedure for Recording and Reporting a Pregnancy

6.2.1 Recording and reporting a Pregnancy to the JRO

- Depending on the safety profile of the IMP it may be important to monitor pregnancies in **female trial participants** receiving an IMP, and occasionally **partners of male trial participants**. Under special circumstances, it may be necessary to monitor the development of the new-born for an appropriate period post-delivery.
- The trial protocol will stipulate the requirements for pregnancy reporting, and any actions to be taken such as stopping trial interventions.
- On the notification of a pregnancy in a trial participant or their partner (if applicable), a member of the trial team must inform the PI.
- The trial specific **Pregnancy Reporting Form** must be completed and forwarded to the JRO **as soon as possible and no later than 24 hours** after the site were made aware of the pregnancy.

Pregnancy Reporting Form must be emailed to the JRO at **sae@ucl.ac.uk**

- In the event that the pregnancy report form is not acknowledged within **3 working days**, the reporter should contact the JRO to confirm receipt.
- The JRO may forward the pregnancy report form, safety reference document and protocol to a sponsor clinician for review and comment on recommended follow-up and tests/procedures to be performed above the protocol to protect the participant/ female partner and the foetus, if deemed appropriate. Recommendations from the sponsor clinician will be forwarded to the CI by the JRO.
- A separate REC approved Patient Information Sheet (PIS) and Informed Consent Form (ICF) (if pregnancy follow-up is not detailed in the original forms) will be supplied to the trial team to consent the participant or partner for follow-up of pregnancy until term or termination.
- The pregnancy report form and associated correspondence should be filed in the ISF.

6.2.2 Follow-up of pregnancy

- Once site are made aware of any updates to the pregnancy including the outcome, (birth or termination) the Pregnancy Reporting Form must be updated and forwarded to the JRO **as soon as possible and no later than 24 hours** after the site became aware of the follow-up information.
- If the pregnancy outcome or an associated adverse event meets the following definition; an **SAE Reporting Form** must also be completed and forwarded to the JRO with the pregnancy follow-up form within 24 hours:
    - Congenital anomaly(ies) in the foetus/child
    - Foetal death or spontaneous abortion
    - Any SAE occurring in the neonate or mother

6.3 Periodic Review of Adverse Events

Periodic review and analysis of trial safety information is important to identify and mitigate any risks associated with the trial interventions and to assess the ongoing risk-benefit of the trial. Below are a number of ways the Investigator can demonstrate oversight of trial safety data.

6.3.1 Review of AE listings

- **Periodic reviews** of listings of AEs from the trial database should be performed by the Investigator.
- Reviews must be **documented**, e.g. minutes/reports from Trial Management Group / Trial Steering Committee meetings.

6.3.2 Reports from Safety Oversight Committees

- For some trials adverse events will be reviewed by an **Independent Data Monitoring Committee** (IDMC) / **Safety Data Monitoring Board** (DSMB).
- The CI should ensure reports are **reviewed** and any actions regarding safety are implemented.

6.3.3 Development Safety Update Report (DSUR)

- The CI and relevant trial staff will be made aware by the JRO when the **data lock point** for the DSUR has been reached.
- The trial staff will work with the JRO Pharmacovigilance Manager to facilitate the production of the report.
- The CI will **review and approve** all safety listings and updates to safety information contained in the report.

6.4 Updates to Reference Safety Information (RSI) Documents

6.4.1 RSI Documents

- The RSI is a list of medical events that defines which reactions are expected for the IMP being administered to clinical trial subjects, and so do not require expedited reporting to the

Competent Authority. It is contained in the **Summary of Product Characteristics (SmPC**) or the **Investigator's Brochure (IB)**. It is important that the RSI is:

- **Identifiable** – clearly defined in the initial Clinical Trial Authorisation (CTA) application cover letter as a specific section in the IB or section 4.8 of the SmPC. The current approved and previous versions of RSI for all JRO managed trials is listed in the JRO DSUR/RSI Tracker and the documents are filed in the PVG section of the Sponsor File for each trial.
- **Approved** – submitted as part of the documentation in the initial CTA application to the regulatory authority, and any changes to the RSI submitted as substantial amendments.
- **Consistent** – only the RSI version approved by the regulatory authority is used by reviewers responsible for assessing expectedness of SARs.

6.4.2 Updates to the IB

- If the IB is prepared by UCL it is highly recommended that it should be updated **annually** after the DSUR Data Lock Point, so it can be submitted to the MHRA (if needed) in line with, or soon after the DSUR submission.
- When an IB is prepared by a drug supplier, the provisions for supplying updates at least annually will be stated in the relevant agreement with the supplier.
- The CI must confirm if the new information in an updated IB impacts the trial and participant safety and if any amendments are required to the protocol, PIS / ICF.
- An updated IB must be submitted to the regulatory authorities as a **substantial amendment** if there is a change to the RSI (new events listed or removed) or other changes likely to have an impact on the safety of the trial participants or conduct of the trial, or if they are otherwise significant. The **new version cannot be used as RSI until it is approved**.

6.4.3 Updates to the SmPC

- When the CI is made aware of an update to a SmPC, they must **review** the document see if the safety profile of the IMP has been altered and impacts on trial process and participant safety (new contraindicated drugs, dosing levels altered etc.), and to see if the RSI has been changed (any new events added or removed from the list of adverse reactions in Section 4.8).
- The CI must confirm if the new information in an updated SmPC requires updates to the protocol, PIS / ICF.
- AN updated SmPC must be submitted to the regulatory authorities as a **substantial amendment** if there is a change to the RSI (new events listed or removed) or other changes likely to have an impact on the safety of the trial participants or conduct of the trial, or if they are otherwise significant. The **new version cannot be used as RSI until it is approved**.

6.5 Overdose Reports

- In the event of an accidental or intentional overdose by a trial participant, the site staff must immediately inform the Investigator and the JRO.

- The **Log of Deviations, Violations, Potential Serious Breaches, Serious Breaches, Urgent safety measures** must be completed and the medical notes, CRF, updated to reflect this information.
- In the event that the overdose is associated with an adverse event, an SAE Reporting Form must be completed detailing the adverse event and the overdose details and forwarded to the JRO **as soon as possible** by email to **sae@ucl.ac.uk**.

6.6 Procedures for Blinded Trials

- The blind for the Investigator and if applicable, for those persons responsible for data-analysis and interpretation of results should be maintained until the trial database is locked.
- However a participant's treatment allocation may need to be unblinded under the following conditions:
  1. Emergency unblinding: Participant experiencing an adverse event and requiring treatment which cannot be given without knowledge of the trial arm the patient was randomised to.
  2. SUSAR unblinding: The JRO requires unblinding of treatment allocation for the submission of a SUSAR report to the MHRA and REC.
- The unblinding procedure is protocol specific and each trial must clearly document their procedure and the location of the unblinding information.
- Refer to the trial specific arrangements outlined in the trial specific **Randomisation, Blinding and Code Break SOP.**

6.7 Other Safety Issues

Safety issues, which might materially alter the current **benefit-risk assessment** of the trial but which do not meet the definition of a SUSAR, may occur during a trial.

Examples are new events related to the conduct of a trial or the development of an IMP likely to affect the safety of subjects, such as:

- an SAE which could be associated with the trial procedures and which could modify the conduct of the trial,
- a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,
- a major safety finding from a newly completed animal study (such as carcinogenicity),
- a temporally halt of a trial for safety reasons and conducted with the same IMP in another country by the same Sponsor,
- in the case of advanced therapy investigational medicinal products, relevant safety information regarding the procurement or the donor.
- recommendations of the Data Monitoring Committee (DMC), if any, where relevant to the safety of the subjects.

The PI/CI must inform the JRO **immediately** should they become aware of any such safety issues. These events/observations are not to be reported as SUSARs, but they might require other action, such as urgent safety measures, substantial amendments or early termination. Where such actions are not taken the JRO should inform the MHRA and REC.

For the reporting of urgent safety measures please refer to the **SOP for the Recording and Reporting of Deviations, Violations, Serious Breaches & Urgent Safety Measures** (JRO/SPON/S15).

6.8 Safety warning and drug alerts

Safety Alerts (from the MHRA and drug suppliers) may be forwarded by the JRO or be sent directly by another organisation to the CI.

The received information must be **reviewed** immediately by the CI or delegated member of the trial team to assess whether any actions are required to protect participant safety. The information must be forwarded to the JRO with any recommendations and what actions (if any) are required.

7. REFERENCES

https://www.ucl.ac.uk/joint-research-office/

ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R2)

European Parliament Directives 2001/20/EC, 2005/28/EC and Regulation 536/2014

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and amended regulations.

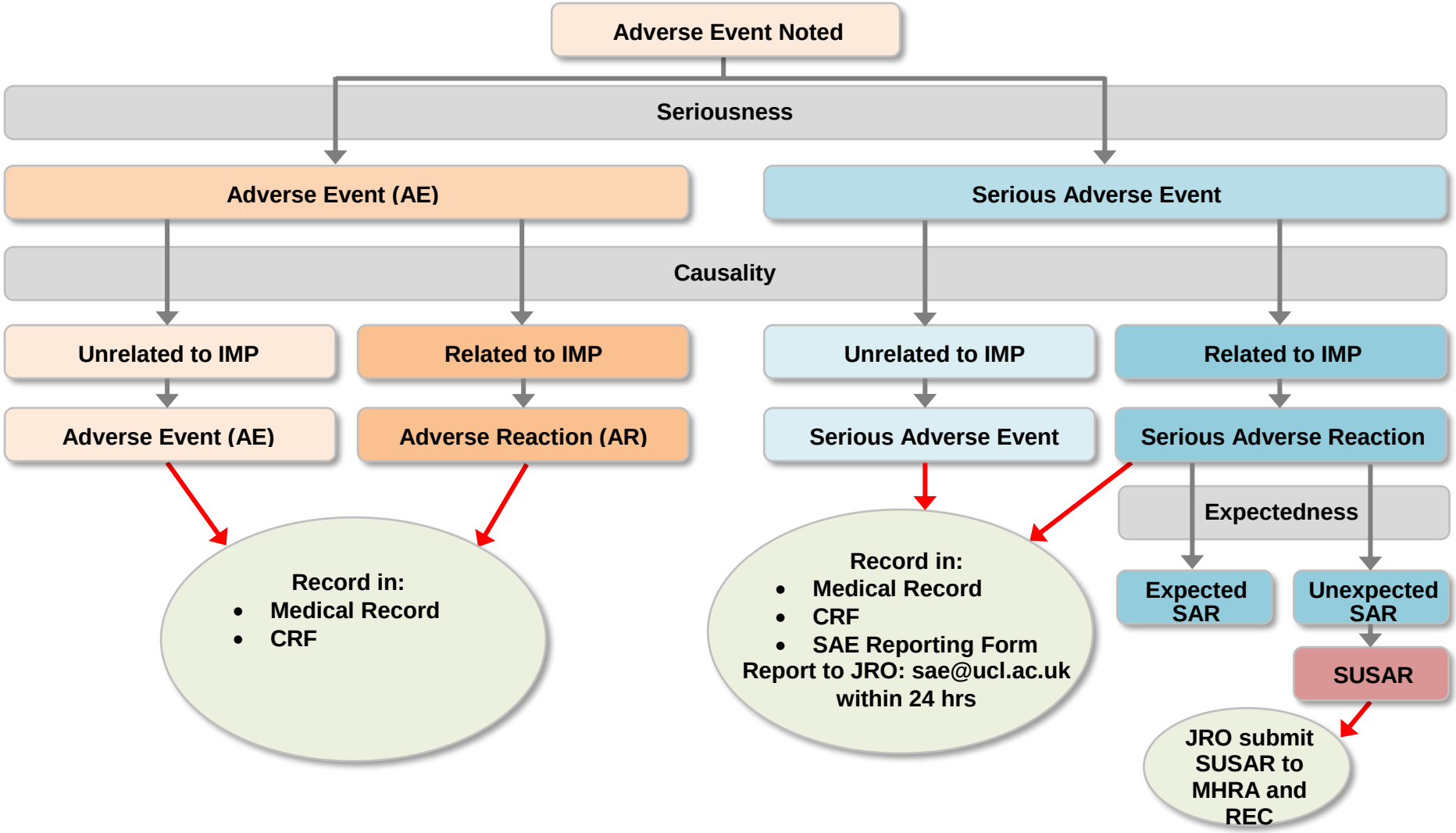
Communication from the European Commission - Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use ('CT-3'), 2011

CTFG Q&A document on Reference Safety Information, Nov 2017

CTFG Recommendations related to contraception and pregnancy testing in clinical trials, V1.1, 21/09/2020

8. APPENDICES

Appendix 1: Adverse Event Assessment, Recording and Reporting Workflow



9. TEMPLATES/LOGS ASSOCIATED TO THIS SOP

None.

10. SOP DISSEMINATION & TRAINING

This SOP will be provided to the PIs prior to, or at initiation at the latest. All staff trial team concerned by this SOP will sign the SOP training log (12. SOP TRAINING LOG) part of this SOP / or add details of the SOP to the “Individual staff SOP and courses log”. These documents should be filed in the ISF.

For existing trials “in progress”: This SOP will be emailed to the PIs and their teams. The trial teams will be requested to read the new SOP and sign the training log.

11. SIGNATURE PAGE

Author and Job Title:	Catherine Manager, Pharmacovigilance Manager
Signature and date:	DocuSigned by: Catherine Maidens 6A859A9CF4EB497... 06/12/22

Authorised by: Name and Job Title	Helen Cadiou, Head of Quality Assurance
Signature and date:	DocuSigned by: Helen Cadiou 9FE319AE9B744D5... 06/12/22

12. SOP TRAINING LOG:

	Name of Staff (Capital letters)**:**	**Job Title:** **Department:**	**Training Date**	**I confirm that I understand & agree to work to this SOP SIGNATURE**	**Name of Trainer** **(if applicable)**	**Signature**	**Date**
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	Name of Staff (Capital letters)**:**	**Job Title:** **Department:**	**Training Date**	**I confirm that I understand & agree to work to this SOP SIGNATURE**	**Name of Trainer** **(if applicable)**	**Signature**	**Date**
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