Standard Operating Procedure (SOP)

Reporting of Adverse Events for CTIMPs Sponsored by St George's

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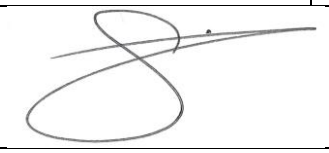
Author:	Georgia Bullock	**Title:**	Research Development and Governance Manager
Approved by:	Subhir Bedi	**Date:**	08/02/2022
Signature of Authoriser			

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The master document is posted on the JRES website and any print-off will be classed as uncontrolled.

Researchers and their teams are responsible for checking the JRES website for the most recent version.
They may print off this document for training and reference purposes.

SOP Chronology		
SOP Version Number:	**Reason for Change:**	**Author:**
V1.0	Original Version	Ailsa Withers
V2.0	To update SOP with new PV procedure and new SOP numbering system	Ailsa Withers
V3.0	To update SOP with new PV procedure adopted by JRO since January 2010 to ensure compliance with PV requirements of the UK Clinical Trials regulations.	Ira Jakupovic

V4.0	To update with new procedure for reporting Adverse Incidents to SGHT Risk Management Department	Ira Jakupovic
V5.0	A typographical error in section 9 corrected to ensure Part 2 of ASR reports line listing of all SARs	Ira Jakupovic
V6.0	Revision of V5.0	Ira Jakupovic
V7.0	Updated in line with current MHRA reporting guidelines; new JREO SOP template; ID issue number and to incorporate new JREO process and procedure	Debbie Rolfe
V7.0	Updated in line with current MHRA reporting guidelines; new JREO SOP template; ID issue number and to incorporate new JREO process and procedure	Debbie Rolfe
V8.0	Updated appendices AE log and SAE reporting form added to the SOP, added definition and clarifications on CI and PI responsibilities. Updated NRES hyperlink in Appendix 8.3	Debbie Rolfe
V9.0	Updated with New Foundation Trust status & Code break for blinded studies	Debbie Rolfe
V10.0	Urgent Safety Information timelines corrected. Updated JREO actions in line with actual office procedures	Debbie Rolfe
V11.0	Reflecting changes in JREO to JRES and job titles and minor changes to the process and deletion of appendices. Also, insertion of associated JRES documents. **Incorporation of JREOSOP0041 and JREOSOP0047 into this SOP.**	Georgia Bullock
V12.0	Addition of SAE/SUSAR reporting to the insurer of sponsored CTIMPs	Georgia Bullock

Associated JRES documents

SOPs	WPDs	Docs	LOGs
JRESGOVSOP0012 Protocol Deviations JRESGOVSOP0011 Management of Amendments StG Sponsored JRESGOVSOP0033 Safety Reporting for Non CTIMP studies	JRESWPD0023 General Research Definitions	JRESDOC0012 SAE Reporting Form JRESDOC0046 DSUR Template	JRESLOG0007 Adverse Events Log JRESLOG0016 Study Training Log UMAL SAE Log

Contents

1. Background

The Sponsor of a Clinical Trial of an Investigational Medicinal Product (CTIMP) is responsible for the ongoing safety evaluation of the IMP and the current Clinical Trials Regulations define the responsibilities for safety reporting of both the Sponsor and the Investigators at the trial sites. The Regulations set out the legal requirements for the recording, management and reporting of Adverse Events (AEs) in clinical trials.

2. Joint Research and Enterprise Services (JRES) Policy

All JRES SOPs will be produced and approved in accordance with the JRES SOP on SOPs and must be used in conjunction with local NHS Trust and University policies and procedures.

The JRES acts as the representative of both St George's University of London (SGUL) and St George's University Hospitals NHS Foundation Trust (SGHFT). St George's will be the official name used on all SOPs to represent either institution acting as Sponsor.

3. Scope

This Standard Operating Procedure (SOP) describes the procedure to be used by all Investigators for the recording and reporting of Adverse Events (AEs), Adverse Reactions (ARs), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur on CTIMPs sponsored by St George's.

It also outlines the procedures to be followed by the Sponsor (JRES) for the management of all AEs, ARs, SAEs, SARs reported by the investigational sites, and the expedited reporting of SUSARs according to regulatory requirements.

Any trial-specific safety reporting requirements must be adhered to in addition to this SOP, as outlined in the trial protocol and/or the SAE Manual (where available).

This SOP outlines the reporting procedure during the allocated University closure days when the JRES is closed, specifically over the Christmas and New Year period.

This SOP outlines the procedure for the reporting of AEs and SAEs for international CTIMPs sponsored by St George's.

Where there may be trial-related responsibilities delegated by the sponsor to a third party (such as a Clinical Research Organisation or a Clinical Trials Unit), an appropriate process/ SOP must be agreed at the sponsorship review stage and fully documented.

This SOP does not describe the procedure for the reporting of **Adverse Incidents** (AIs) within St George's University Hospitals NHS Foundation Trust. Research-related AIs must be reported as per the Trust's Adverse Incident policy.

This SOP also does not cover safety reporting for non-CTIMP studies. That is covered by JRESGOVSOP0033.

4. Definitions

For general research-related acronyms used in this SOP, refer to General Research Definitions Working Practice Document (JRESWPD0023).

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP whether or not related to that IMP.

Adverse Reaction (AR)

Any noxious and unintended response to an IMP where a causal relationship between the IMP and an AE cannot be ruled out.

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

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly or birth defect

Please 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, subjects do not need to be hospitalised overnight to meet the hospitalisation criteria. Hospitalisation for an elective procedure or for a pre-existing (prior to study entry) condition which has not worsened is not defined as an SAE.

Important medical events that may jeopardise the subject or may require intervention to prevent one of the outcomes listed above should also be considered as serious, eg: overdoses (accidental or intentional); pregnancy (of subject or their partner); AE and/or laboratory abnormalities which are listed in the trial protocol as critical to safety evaluations and require reporting.

Suspected Serious Adverse Reaction (SSAR)

An AR that is classed in nature as serious and which is consistent with the information about the IMP listed in the relevant reference documentation, ie: the Summary of product characteristics (SmPC) for a licensed medicinal product being used according to licensed doses and indications or an Investigator's brochure (IB) for any other IMP or for an IMP being used outside of its SmPC.

Unexpected Adverse Reaction (UAR)

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (SmPC or IB).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is classified as both serious and unexpected.

Other Serious Safety Issues

Other safety issues which might materially alter the current risk-benefit assessment of an IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the trial also need to be considered serious. For example:

- An increase in the rate of occurrence or qualitative change of an expected SAR which is judged clinically important.

- Post study SUSARs that occur after the patient has completed a clinical trial and are reported by the Investigator to the Sponsor.
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects.
- 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 a life-threatening disease.
- Any anticipated end or temporal halt of a trial for safety reasons and conducted with the same IMP in another country by the same Sponsor.
- Recommendations of the Data Monitoring Committee (DMC), if any, where relevant for the safety of subjects.
- Any pregnancies that occur in clinical trial subjects as soon as the investigator becomes aware of the event. It may be necessary to monitor the pregnancy of a woman whose male partner is the trial subject.

Causality

Any causality assessments must be made by the PI or the Sponsor-agreed delegated medically qualified individual. The study delegation log must reflect this.

The definitions below can be used:

- *Unrelated:*

There is no evidence of causal relationship to the Investigational Medicinal Product

- *Related:*

There is evidence of causal relationship to the Investigational Medicinal Product.

Events relating to placebo or reference drugs must also be reported.

Expectedness

The approved Reference Safety Information (RSI) i.e. Investigator Brochure or Summary of Product Characteristics MUST be used to determine Expectedness.

- *Expected*

The event is expected based on the information contained in the Investigator Brochure and/or the Summary of Product Characteristics.

- *Unexpected*

The event is Unexpected based on the information contained in the Investigator Brochure and/or the Summary of Product Characteristics.

Events relating to placebo or reference drugs must be reported.

Events leading to the death of a study participant need to be reported to the Sponsor immediately once the Investigator becomes aware of the event, unless death is classified as an expected event and therefore exempt from reporting. Events which are exempt from reporting must be detailed in the approved trial protocol.

Urgent Safety Measure

It may be necessary to undertake a procedure that is not defined in the protocol but has to be taken without any authorisation from the MHRA and/or REC, in order to protect the trial subjects from any immediate hazard to their health or safety. The PI/CI/Lab will need to report this immediately to the JRES and submit a summary of the discussions with the Competent Authority within 3 days to the MHRA with an expected timeline of amendment preparation. The JRES/CI must co-ordinate effective communication to ALL key staff at all participating sites.

Please see JRESGOVSOP0011 'Management of Amendments StG Sponsored'.

Adverse Incident

An 'adverse incident' is any event, circumstance, activity or action which has caused, or has been identified as potentially causing harm, loss or damage to patients, members of the public or staff. This includes breaches of confidentiality, serious adverse events, serious adverse reactions, which requires a hospital admission and has a severity grading of severe or critical. This should be reported as per the relevant local site/Trust procedure.

5. Responsibilities

This SOP is to be followed by all investigators of St George's sponsored CTIMPs and their trial teams; the JRES Governance team, including the Clinical Research Associates (CRAs) and the Research Development and Governance Manager (RDGM); Research Pharmacy staff when providing cover for the JRES.

a) It is the responsibility of the PI to:

- Keep records of all AEs that occur in trial subjects in accordance with the trial protocol.
- Record the delegation of safety reporting to another suitably qualified team member on the Delegation of Duties log, if applicable.
- Train and update other team members on the use of the IMP and any new information about the IMP. All training must be documented on the appropriate form.

- Record all SAEs/AEs/ARs in the patient's medical notes, in the CRF and the AE Reporting Log.
- Assess each AE for seriousness/intensity, causality and expectedness.
- Review AE logs regularly and escalate any that have increased frequency or intensity to the JRES.
- Record any SAEs/SARs/SUSARs on the SAE/SAR form and send the report to the CI/ Research Team and also the JRES (adverseevents@sgul.ac.uk) immediately or at least within 24 hours of becoming aware of the event.
- Provide follow-up SAE/SAR/SUSAR information within 14 days of any new information received using the SAE/SAR form, marking the form as 'Update 1', 'Update 2' etc. The SAE/SAR/SUSAR must be followed up until resolution according to the timelines agreed in the trial-specific monitoring plan. The JRES email address (adverseevents@sgul.ac.uk) should be copied in all communication regarding SAEs.
- Report any SAEs which meet the definition of an Adverse Incident to the Trust via Datix or, for other Trusts, as per their incident reporting policy.
- File all safety reporting documents, reports and information in the ISF in the Pharmacovigilance section.
- Any clinical reports relating to the SAE/SAR/SUSAR that are sent with the SAE Reporting form should be anonymised with the patient's study ID and SAE reference number added.

b) It is the responsibility of the CI to:

- Ensure that the protocol references any expected AEs/ARs where known and defines those which do not require reporting.
- Review all SAE/SAR/SUSAR reports sent by a study site to confirm causality and expectedness and to follow up with the site if any information is missing on the report which is required to complete this review. The CI may choose to delegate this task to another appropriately trained member of the study team – this must be recorded on the Study Delegation Log.
- Inform the JRES immediately if a SUSAR is confirmed **in order that the SUSAR can be reported within the required timelines.**
- Ensure that the JRES receives all final SAE/SAR reports.

- Review and update the IB and IMP dossiers annually and request these documents from IMP manufacturers where applicable. Any updates to this information must also be communicated to the JRES and the Pharmacy departments at the participating sites and the updated documents must be filed in the ISF.
- Ensure confirmed SUSARs and any Urgent Safety Measures are communicated to all participating trial sites.

c) It is the responsibility of the JRES (Sponsor) to:

- Ensure that the CI, PI, and their team are aware of the requirements and documentation for safety reporting.
- Check that all AEs have been accurately recorded and all SAEs have been reported to the Sponsor, during monitoring visits.
- Check the JRES Adverse Event email (adverseevents@sgul.ac.uk) inbox daily for reported SAEs and all communication related to reported SAEs.
- Acknowledge the receipt of an SAE report to the reporter within 1 working day via email.
- Ensure that the CI/Research Team reviews SAE reports within 72 hours to allow for expedited reporting of any SUSARs.
- Report SUSARs to the MHRA as per MHRA requirements.
- Provide reports of SAEs/SUSARs to the insurer (UMAL).
- Maintain all paper and electronic records for pharmacovigilance within the JRES.
- Update the CI at monthly intervals to ensure medical oversight of SAEs/pharmacovigilance.

6. Procedure

6.1 Investigator Procedure

a) **Adverse Events:**

- The Investigator must complete all required information on the AE Reporting log for all AEs.
- AE logs must be submitted to the CI team bi-monthly, copying in the JRES. It is essential that these do not contain information that could compromise, where applicable, JRES and/or the CI blinding.

b) **Serious Adverse Events:**

- SAEs must be reported on the SAE reporting form to the **CI and Sponsor** immediately or at least within 24 hours of the Investigator becoming aware of the event. The investigator

must ensure that all SAEs forms are legible and are completed as fully as possible at the point of reporting.

- SAE reports must be emailed to the JRES Adverse Event inbox adverseevents@sgul.ac.uk The faxing of reports is no longer permitted.
- The first submission of an SAE reporting form must clearly be marked as 'initial' Any subsequent SAE reporting forms for that event (including that of corrections) must be clearly marked as 'update' and numbered sequentially.
- Any amendments, corrections or additional information must be dated and initialled.
- All SAEs must be signed off by the PI at site (or appropriately delegated study team member) before review by the CI (or appropriately delegated study team member).

c) **SUSARs:**

- SUSARs must be reported to the JRES at least within 24 hours of notification of the event. **Not all fields require completion at this point**. However, any information that is missing must be forwarded to the JRES at the earliest opportunity.
- Follow-up information for SUSARs must be sent to the JRES within 7 days of the initial report.

If an SAE/SUSAR report is reported outside of the defined reporting guidelines, according to the protocol and regulatory requirements, a reason should be provided to the JRES and the event recorded on the protocol deviation form JRESDOC0061 in accordance with JRESGOVSOP0012.

6.2 JRES Procedure

a) The CRA or RDGM will ensure that the inbox for Adverse Events is checked on a daily basis for reported SAEs. They will acknowledge receipt of the SAE report to the sender and research team, copying in any other relevant personnel.

b) For double-blinded studies, the code break should be performed in accordance with the protocol instructions ensuring the Investigator is not inadvertently unblinded.

c) If the Investigator has assessed the event as serious, unexpected and the causality has been assessed as definite, possible, probable or not assessable, the SAE becomes a SUSAR. This must be **reported as a SUSAR** if the CI agrees with the assessment. If the CI is satisfied that the event is not a SUSAR, the Sponsor can downgrade the event to an SAE.

d) SUSARs must be reported to the MHRA.

e) Any **fatal or life threatening SUSARs** must be reported to the MHRA as soon as possible, but no later than **7 days** after the JRES was made aware of the SUSAR. Any non-fatal or non-life threatening SUSARs must initially be reported within 15 days. Follow-up reports must be sent no later than **8 days** after the initial report.

f) SUSAR reports must be sent to the relevant Ethics Committee accompanied by the CTIMPs Safety Report form (available on the HRA website) with option 1 selected. https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/. A cover letter should also be sent with the signed form and the SUSAR report.

g) A copy of the ethics notification and (upon receipt) the ethics confirmation of receipt must be forwarded to the CI to be filed in the TMF.

h) The electronic SUSAR report will be sent to the CI to facilitate notification/escalation to all other site investigators.

i) SAEs/SUSARs outside of the reporting window, as defined either by the protocol or regulatory body, must be noted on the protocol deviation log. On the line-listing in the annual DSUR (JRESDOC0046), the late report should be noted.

j) All reports and documentation for SAEs and SUSARs will be filed in the sponsor trial files.

k) All SAEs/SUSARs/SARs should be collated on the CTIMP SAE Spreadsheet.

l) A report of all SAEs/SUSARs must be provided to the insurer, UMAL, for all CTIMPs insured by them, on a quarterly basis, using the UMAL SAE Log available in the shared drive. Any fatal or life-threatening SAEs must be provided to them as soon as possible following notification.

Sponsor Cover for SAEs/SUSARs

a) During periods when the JRES is closed (specifically only the University closure days over Christmas and New Year), arrangements must be put in place for SAE forms to be reviewed and acknowledged and for any SUSARs to be reported to the MHRA.

b) Cover may be provided by the Research Pharmacy team at St George's with support from a nominated JRES governance member of staff. If this is not possible, alternative arrangements must be made.

c) The agreed cover must be communicated to the CI and PI for each current sponsored CTIMP with the relevant contact details.
d) The Adverse Event email address inbox must be auto-forwarded to the Pharmacy team's generic email for the agreed time period.
e) Detailed instructions and contact details must be provided to the Pharmacy on how to manage the SAE reports received, along with any relevant SOPs, guidance and forms.
f) Any communication/emails relating to SAEs received by the Pharmacy during this period should be provided to the JRES on their return to work.

AE Reporting for International CTIMPs

a) It is expected that any country that is selected for participation or contribution to a CTIMP sponsored by St George's will, as a minimum requirement, conduct all trial-related activities to the standards described within ICH GCP.
b) Local PIs will have knowledge of local procedures and requirements in their country and these will be agreed to ensure that the responsibilities of the Sponsor are met, and that local investigators are aware of their responsibilities for the recording and reporting of adverse events to meet country-specific requirements.
c) For international CTIMPs sponsored by St George's, all SAEs should be reported to the Sponsor within 24 hours of notification and a line-listing of all AEs should be provided to the Sponsor on a monthly basis.
d) Local reporting procedures will be checked at monitoring visits as per the monitoring plan, to ensure that they are being followed.
e) The CIOMS reporting form is the widely accepted form: https://cioms.ch/wp-content/uploads/2017/05/cioms-form1.pdf

7. References

ICH GCP and Clinical Trials Regulations:
https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/

St George's DATIX system:
http://stginet/Units%20and%20Departments/Governance/Risk%20Management/Advers%20Incident%20Reporting/Adverse%20Incident%20Reporting.aspx

MHRA eSUSAR system: https://esusar.mhra.gov.uk

HRA Safety Reporting for CTIMP studies:

http://www.hra.nhs.uk/research-community/during-your-research-project/safety-reporting/

ICH E2A:
https://www.ema.europa.eu/en/ich-e2a-clinical-safety-data-management-definitions-standards-expedited-reporting

CIOMS:
https://cioms.ch/pharmacovigilance/

8. Appendices

Appendix 1: Appendix 1: NIHR Decision Tree for Adverse Event Reporting - CTIMPs

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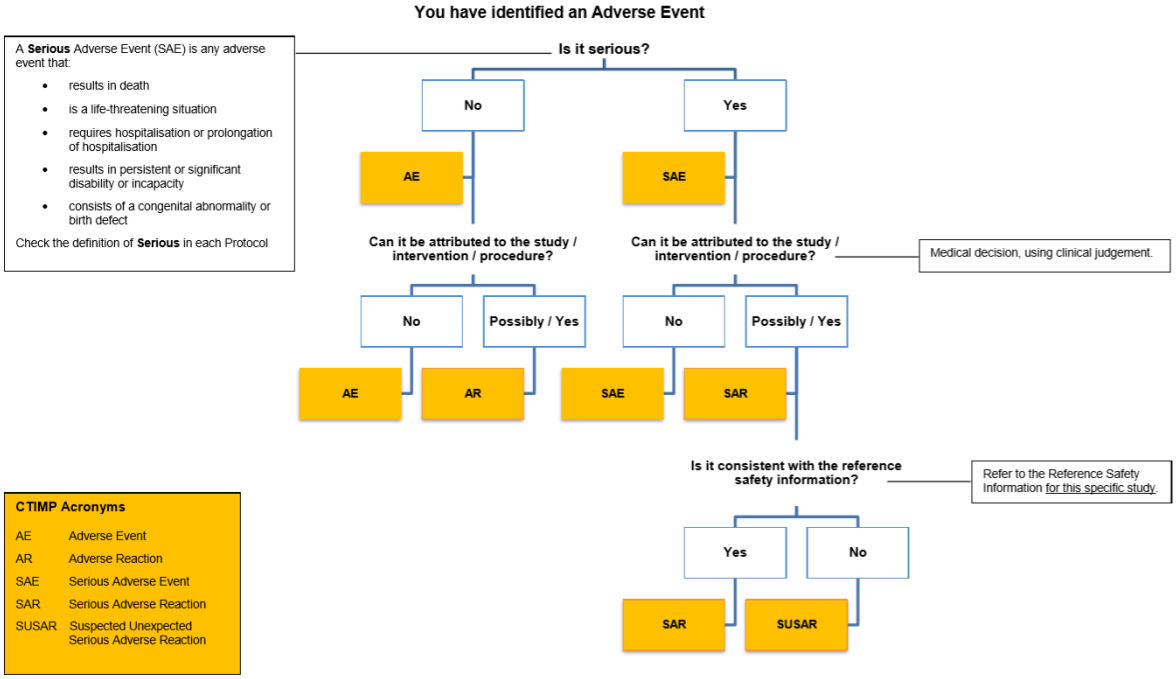
NIHR | National Institute for Health Research

Decision Tree for Adverse Event Reporting – CTIMPs



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