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Standard Operating Procedure (SOP)

Safety Reporting for Clinical Investigations of Medical Devices Sponsored by St George's

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

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SOP Chronology		
SOP Version Number:	**Reason for Change:**	**Author:**
V1.0	Original Version	Georgia Bullock

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Associated JRES Documents

SOPs	WPDs	Docs	LOGs
JRESGOVSOP0012 Protocol and GCP Deviations JRESGOVSOP0011 Management of Amendments StG Sponsored JRESGOVSOP0006 Reporting of AEs for CTIMPs	JRESWPD0023 General Research Definitions	JRESDOC0012a SAE Reporting Form for Medical Devices	JRESLOG0007 Adverse Events Log JRESLOG0016 Study Training Log

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1. Background

Clinical Investigations of non-UKCA/CE UKNI/CE-marked medical devices, and UKCA/CE UKNI/CE-marked devices that have been modified or are to be used for a new purpose/indication, require review by the MHRA. These Investigations require the ongoing safety evaluation of the device and the reporting of Adverse Events (AEs) by the Sponsor, in collaboration with the manufacturer of the device.

In order to comply with the appropriate legislation, including the current Medical Device Regulations, all researchers must be aware of the definitions and procedures in relation to the recording and reporting of AEs for Clinical Investigations of Medical Devices.

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 Device Events (ADEs), Serious Adverse Events (SAEs), Serious Adverse Device Events (SADEs), Unanticipated Serious Adverse Device Events (USADEs) and Anticipated Serious Adverse Device Events (ASADEs) that occur in Clinical Investigations of Medical Devices which are sponsored by St George's.

This SOP applies to Clinical Investigations of any medical device requiring an MHRA Letter of No Objection (ie: non-UKCA/CE UKNI/CE-marked medical devices and UKCA/CE UKNI/CE-marked devices that have been modified or are to be used for a new purpose/indication).

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This SOP outlines the procedures to be followed by the Sponsor (JRES) for the management of all AEs, ADEs, SAEs, SADEs reported by the investigational sites, and the expedited reporting of SAEs and USADEs according to regulatory requirements.

MHRA safety reporting requirements are set out in the Letter of No Objection for each individual Clinical Investigation, and these must be adhered to at all times, in addition to this SOP. The requirements set out in the Pharmacovigilance section of each individual trial protocol must also be adhered to.

Where trial-related responsibilities are 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 Adverse Event reporting for clinical trials involving Investigational Medicinal Products (CTIMPs). Please refer to JRESGOVSOP0006.

This SOP does not describe the procedure for the reporting of **Adverse Incidents** (AIs) within St George's University Hospitals NHS Foundation Trust Risk Management Database "Datix" by Investigators for all clinical research occurring within the Trust. AIs must be reported as per Trust policy. The 'Adverse Incidents Reporting Policy and Procedures' can be accessed via the Trust intranet.

4. Definitions

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

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device. This definition includes events related to the investigational device or the comparator.

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Adverse Device Event (ADE)

An 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.

Serious Adverse Event (SAE)

Any Adverse Event that:

- resulted in death, injury or permanent impairment to a body structure or a body function.
- led to a serious deterioration in health of the subject, that either resulted in:
  - a life-threatening illness or injury.
  - a permanent impairment of a body structure or a body function.
  - in-patient hospitalisation or prolongation of an existing hospitalisation.
  - a medical or surgical intervention to prevent life threatening illness.
- led to foetal distress, foetal death or a congenital abnormality 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.

Device deficiencies that might have led to a serious adverse event where a suitable action had not been taken or an intervention had not been made, or if circumstances had been less fortunate, are reported 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.

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Serious Adverse Device Effect (SADE)

Any adverse device effect that results in any of the consequences characteristic of a Serious Adverse Event.

Device Deficiency

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, user error or inadequacy in the information supplied by the manufacturer.

Unanticipated Serious Adverse Device Effect (USADE)

A Serious Adverse Device which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Anticipated Serious Adverse Device Effect (ASADE)

An effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Other Serious Safety Issues

Other safety issues which might materially alter the current risk-benefit assessment of a medical device or that would be sufficient to consider changes in the device 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 SADE which is judged clinically important.
- Post study USADEs 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 device and likely to affect the safety of the subjects.
- An SADE 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 a device used for a life-threatening disease.
- Any anticipated end or temporal halt of a trial for safety reasons and conducted with the same device 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.

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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 any causal relationship to the medical device
Unlikely	The relationship with the use of the investigational medical device seems not relevant and/or the event can be reasonably explained by another cause
Possible	The relationship with the use of the device is weak but cannot be ruled out completely
Probable	The relationship with the investigational medical device seems relevant and/or the event cannot be reasonably be explained by another cause
Related	The event is associated with the investigational medical device beyond reasonable doubt

Expectedness

- *Expected*

The event is expected based on the information contained in the Investigator Brochure, the Protocol and/or Risk Analysis Report.

- *Unexpected*

The event is unexpected based on the information contained in the Investigator Brochure, the Protocol and/or the Risk Analysis Report.

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,

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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 Clinical Investigations of Medical Devices and their trial teams; the JRES Governance team, including the Clinical Research Associates (CRAs) and the Research Development and Governance Manager (RDGM).

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 medical device and any new information about the device. All training must be documented on the appropriate form.
- Record all SADEs/ADEs/SAEs/AEs 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/SADEs/USADEs on the SAE/SADE 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/SADE/USADE information within 7 days of any new information received using the SAE/SADE form, marking the form as 'Update 1', 'Update 2' etc. The SAE/SADE/USADE 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/SADE/USADE that are sent with the SAE Reporting form should be anonymised with the patient's study ID and SAE reference number added.

It is the responsibility of the CI to:

- Ensure that the protocol references any expected AEs/ADEs where known and defines those which do not require reporting.
- Be aware of the safety reporting requirements for the study, as set out in the MHRA's Letter of No Objection.

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- Review all SAE/SADE/USADE reports sent by a study site to confirm causality and expectedness and to sign off the reports once reviewed. The CI must also 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 qualified/trained member of the study team – this must be recorded on the Study Delegation Log.
- Inform the JRES immediately if a SAE, SADE or USADE is confirmed **in order that the USADE can be reported within the required timelines.**
- Ensure that the JRES receives all final SAE/SADE/USADE reports.
- Review and update the IB annually and request these documents from medical device manufacturers where applicable. Any updates to this information must also be communicated to the JRES and any relevant departments at the participating sites and the updated documents must be filed in the ISF.
- Ensure confirmed USADEs and any Urgent Safety Measures are communicated to all participating trial sites.

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/SADEs/USADEs have been reported to the Sponsor, during monitoring visits.
- Check the JRES Adverse Event email (adverseevents@sgul.ac.uk) inbox at least once a day, for reported SAEs/ADEs/USADEs and all communication related to reported events.
- Acknowledge the receipt of an SAE/SADE/USADE report to the reporter within 1 working day via email.
- Ensure that the CI/Research Team reviews SAE reports within 24 hours to allow for expedited reporting of any SAEs/SADEs/USADEs.
- Report individual SAEs/SADEs/USADEs to the MHRA as per the MHRA requirements and as per the Letter of No Objection.
- Provide quarterly summary reports of SAEs to the MHRA as per their requirements.
- 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

Adverse Events (AEs):

- The Investigator must complete all required information on the AE Reporting log for all AEs. All AEs must be fully recorded.

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- 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.

SAEs/SADEs/USADEs:

- SAEs/SADEs/USADEs must be reported on the SAE Reporting Form (JRESDOC0012a) 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 SAE forms are legible and are completed as fully as possible at the point of reporting.
- SAE/SADE/USADE reports must be emailed to the JRES Adverse Event inbox adverseevents@sgul.ac.uk.
- This inbox will be checked at least once a day by the JRES and they will acknowledge receipt of the SAE/SADE report to the sender and research team, copying in any other relevant personnel.
- For double-blinded studies, the code break should be performed in accordance with the protocol instructions, ensuring the Investigator is not inadvertently unblinded.
- The first submission of an SAE reporting form must clearly be marked as 'initial' Follow-up reports should be provided within **14 days** of the initial report. Follow-up information for USADEs must be provided to the JRES within **7 days** of the initial report.
- 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/SADEs/USADEs 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).
- If an SAE/USADE 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 a Protocol Deviation form, in accordance with JRESGOVSOP0012.
- All individual SAEs/SADEs and USADEs **must be reported to the MHRA**. Any **fatal or life threatening** SAEs, SADES or USADEs must be reported to the MHRA as soon as possible, but no later than **2 calendar days** after the JRES being made aware of the event. Any other SAEs/SADEs/USADEs must initially be reported as soon as possible, but no later than **7 calendar days**. Follow-up reports must be sent no later than **7 days** after the initial report.
- SAEs/SADEs/USADEs should be reported to the MHRA using the MEDDEV 2.7/3 reporting Excel spreadsheet (available online) and the completed spreadsheet should be submitted via the MORE portal: Sign in | MORE (mhra.gov.uk).
- A quarterly summary report of all SAEs must be provided to the MHRA, according to their requirements (Notify the MHRA about a clinical investigation for a medical device - GOV.UK (www.gov.uk)).
- Any additional reports/summaries requested in the MHRA's Letter of No Objection must be provided to the MHRA as detailed in the letter.

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- SAEs/SADEs/USADEs must also be reported to the device manufacturer in accordance with any trial agreements.
- SAEs/SADEs that are related to any of the research procedures and are unexpected should be emailed to the REC no later than 15 calendar days from notification, using the form here: Safety reporting - Health Research Authority (hra.nhs.uk). A cover letter should also be sent with the signed form and the report.
- 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.
- The electronic USADE report will be sent to the CI to facilitate notification/escalation to all other site investigators, where applicable.
- SAEs/SADEs/USADEs reported outside of the reporting window, as defined either by the protocol or regulatory body, must be noted on the protocol deviation log.
- All reports, correspondence and documentation for SAEs, SADEs and USADEs will be filed in the sponsor trial files and in the TMF.
- All SAEs/USADEs/SADEs should be collated on an SAE/SADE Spreadsheet by the JRES.

7. References

Notify the MHRA about a clinical investigation for a medical device - GOV.UK (www.gov.uk)

https://ec.europa.eu/docsroom/documents/16477/attachments/2/translations/en/renditions/native

Safety reporting - Health Research Authority (hra.nhs.uk)

8. Appendices

None.

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