

Joint Research Management Office Standard Operating Procedure for:

Pharmacovigilance and Device Safety Reporting (Process for the Sponsor and Coordinating Investigator)

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Purpose and Scope

This standard operating procedure (SOP) outlines the actions and responsibilities of the Joint Research Management Office (JRMO) regarding safety reporting for Medicines and Healthcare products Regulatory Agency (MHRA) regulated Clinical trials of Investigational Medicinal Products (CTIMPs), Advanced Therapy Investigational Medicinal Products (ATIMPs) and Clinical Investigations.

This SOP will identify and standardise the process for receiving, logging, and acknowledging reportable safety events and pregnancies for studies sponsored by Barts Health NHS Trust (Barts Health) or Queen Mary University London (Queen Mary).

The JRMO research database application (ReDA) is used to collect and record pharmacovigilance (PV) and safety events for sponsor oversight purposes only. This function is referred to as the PV desk in this SOP and includes monitoring of the PV safety email inbox. PV is managed by the JRMO during working hours only.

Medical assessment, trends, safety signals and data collection of events for statistical analysis are the responsibility of the Coordinating Investigator (CI).

Abbreviations:

AE	Adverse Event
AESI	Adverse Event of Special Interest
ASADE	Anticipated Serious Adverse Device Effect
ATIMP	Advanced Therapy Investigational Medicinal Products
Barts Health	Barts Health NHS Trust
CRF	Case Report Form
CI	Coordinating Investigator
CIP	Clinical Investigation Plan
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSUR	Development Safety Update Reports
GCP	Good Clinical Practice

IB	Investigator's Brochure
IMP/nIMP	Non/Investigational Medicinal Product
JRMO	Joint Research Management Office
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
IMP/nIMP	Non/Investigational Medicinal Product
PV	Pharmacovigilance
QA	Quality Assurance
Queen Mary	Queen Mary University of London
ReDA	Research Database Application
RSI	Reference Safety Information
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOG	Sponsor Oversight Group
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
USADE	Unanticipated Serious Adverse Device Effect
USM	Urgent Safety measures

SOP Text:		
	Responsibility	Activity
Designing safety reporting procedures.		
1.	CI	When designing the study, ensure that the protocol or Clinical Investigation Plan (CIP) contains comprehensive information on safety reporting. Define process for periodic review of Adverse Events (AE) and (if applicable) device deficiencies. Ensure systems are in place to report Serious Adverse Events (SAE) and (if applicable) device deficiencies within 24-hours to sponsor. The CI must ensure that there are systems in place for locations to report safety events and (if applicable) device deficiencies within 24 hours of becoming aware of the event Confirm the arrangements for managing pregnancies and describe them in the protocol or CIP. For CTIMPS and ATIMPS: When designing the study, ensure that the reference safety information (RSI) is clearly defined in the protocol/CIP and on the cover letter to the MHRA when submitting the Clinical Trial Application.

		For guidance assessing and reviewing the RSI see Associated Document 1: RSI guidance. Agree review & update processes with the Good Clinical Practice (GCP) and Governance Manager. Arrangements should include how the CI will access the most current RSI. The RSI must be reviewed periodically and as a minimum annually in preparation for Development Safety Update Reports (DSUR) submission. The RSI log template (Template 1) can be used to document this review. Failure to document this RSI review by CIs will be deemed a non-compliance with the potential escalation to the JRMO Sponsor Oversight Group (SOG). For International studies: New versions of the Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC), which include a change to the RSI, must be approved by the sponsor before submission for regulatory approval, and, if the study is UK-relevant, must be submitted in parallel to the UK and non-UK competent authorities. This is to ensure that the same version of the RSI is relevant in all countries during the DSUR reporting period. https://www.jrmo.org.uk/performing-research/standard-operating-procedures-sops/sop-26d/
2.	JRMO GCP & Governance Managers and Contract and Costing Teams	If applicable, agree safety reporting requirements with the Investigational Medicinal Product (IMP) or device manufacturer. These arrangements will not always be required for CTIMPs but may be requested by an IMP supplier and should be agreed early in the development of the study (ideally at the funding agreement stage) and defined in the contract between the sponsor and the supplier. For Clinical investigations: The sponsor should delegate the manufacturer responsibility for assessing received Unanticipated Serious Adverse Device Effect (USADE) and device deficiency reports and for reporting them to the MHRA when required, unless otherwise agreed with the JRMO GCP & Governance manager.
3.	CI	Prepare Safety Reporting Systems JRMO Reporting Forms must be used to report SAEs or device deficiencies. Refer to the following associated documents for templates: • SOP 26a, Associated Document 2: CTIMP and ATIMP. • SOP 26d, Associated Document 2: For Clinical Investigations. If Adverse Event of Special Interests (AESI) are described in the Protocol, ensure a study specific & appropriate AESI form is created - see Template 2 AESI form. If pregnancy reporting is required, the pregnancy reporting form (SOP 26a associated document 3) must be used. Any modifications to these templates must be agreed in writing by the JRMO before use. The CI must ensure that all safety reporting and reference information is made available to locations.

		This system should require the CI/Sponsor medical assessor to review events in a within 72 hours of receiving the SAE.
4.	CI/ delegated Medical Assessor/ SOG	Ensure the Medical Assessor role is fulfilled. The CI or a medically qualified individual is delegated by the sponsor to be the PV/device safety medical assessor. The CI must ensure locations are aware of the requirement to report safety events, AESI and pregnancies to the JRMO. If the CI fails to comply with PV/Safety reporting timelines or provide adequate CI oversight as outlined in SOP 26a, this will be logged as a Non-Compliance as per SOP 31 Non-Compliance. Continuous non-compliances will be escalated in accordance with the escalation policy, commencing with the Associate Director of Research Quality and the SOG at the JRMO. Unless otherwise formally agreed and documented through a written agreement by the sponsor and a delegated body, the sponsor is responsible for ensuring that all relevant information about 'UK-relevant' Suspected Unexpected Serious Adverse Reaction (SUSAR), and reportable device events are reported to the competent authority (MHRA).
5.	CI and GCP & Governance manager	Ensure the JRMO is able to unblind events where applicable. When a participant on a blinded study has a SUSAR or reportable device effect, the JRMO as sponsor must be able to unblind prior to submitting the event report to regulatory agencies. This process should be clearly documented in the protocol/CIP and detailed in a study specific unblinding SOP. Comparator drugs are considered IMPs. In the case of a SUSAR arising from a comparator drug it must be reported to the sponsor, who is also obliged to report to the MHRA. Events associated with a placebo or sham procedure will usually not satisfy the criteria for an Adverse Reaction (AR) and therefore will not be subject to expedited reporting. However, where SUSARs or reportable device effects are associated with the placebo or sham procedure, the CI must report to the sponsor who will notify the competent authority.
6.	Senior GCP & Compliance Manager/ delegate	Assign a JRMO Clinical Trial Monitor/Clinical Trial Facilitator to manage the PV-inbox. Ensure the Clinical Trial Monitor/ Clinical Trial Facilitator is appropriately trained prior to being assigned to the PV desk and adequately supported throughout. Ensure the PV desk is appropriately supported, managed, and covered during business hours and with appropriate cover during annual leave/Public holidays. Ensure allocated staff have access to the PV safety email inbox.
Processing Safety reports		
7.	Clinical Trial Monitor/Clinical Trials Facilitator	Check the PV inbox for new correspondence at least once every working day, all new events should be acknowledged within 2 working days and fully logged within 5 working days.

	The JRMO will process and log the following events for CTIMPs & ATIMPS: SAEs, SUSARs, AESI, and Pregnancies. The JRMO will process the following events for Clinical Investigations: SAEs, Serious Adverse Device Effects (SADE), Anticipated Serious Adverse Device Effect (ASADE), USADE, AESI, reportable Device Deficiencies, and Pregnancies. Acknowledging the event • Ensure submission email is accompanied by a SAE or device safety report form. • Ensure the attachment can be open and is legible • Identify and flag any SUSARs, SADEs, USADEs and device deficiencies that could have caused SADEs, immediately notify the allocated GCP & Governance Manager (or, if absent, either GCP & Governance Manager or if both are absent the Quality Assurance (QA) Manager). • Email Study coordinator, Investigator and sender to confirm receipt. Save this email as evidence that the above has been completed Fully logging the event Ensure forms are clear and complete. Follow up with the study coordinator promptly for any missing information, or for incorrect or incomplete relatedness or expectedness assessments. Log the event within ReDA's Post Approval tab using the above principles (see associated document 2). Check whether the event term is an appropriate Medical Dictionary for Regulatory Activities (MedDRA) preferred term. If it is not, then suggest an appropriate MedDRA preferred term for researcher to confirm <u>Expectedness</u> Expectedness remains CI/Medical Assessor responsibility however for completeness review, if the event is assessed as 'related', review RSI approved at time of the event and confirm JRMO agreement that the event is unexpected or expected. All submitted forms must be saved into the "Indemnity" folder using the same format name used in ReDA: • Sub 'Study participant number/ID', SAE 'MedDRA term (Event name)', JRMO 'date SAE received by JRMO/dd-mm-yy' • Example: Sub R055_SAE Portal Vein Thrombosis_JRMO_21.01.2016 Upload initial/follow up SAE forms onto the 'Safety' section on the 'Documents' tab in ReDA. https://www.jrmo.org.uk/performing-research/standard-operating-procedures-sops/sop-26c/ Issue formal confirmation of receipt of event notification. Feedback should be sent to the research team, stating the name of the logged SAE and whether there are any missing information or signatures that have still to be received. If a new MedDRA term has been assigned to the event, state the term, and ask the CI/Medical assessor to confirm agreement. Confirm whether the event has been assessed as expected or unexpected (via RSI) and follow up with CI/medical assessor for further
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		discussion if needed. The CI/medical assessor review should be received within 72 hours being aware of the event. Receipt and SAE content feedback can be combined with the initial confirmation of receipt email where appropriate.
8.	Clinical Trial Monitor/ Clinical Trial Facilitator	Follow up events. Follow up details will be logged in the existing ReDA entry where the initial report was logged. When significant new information is received as part of a follow up, the event should be reassessed to see if it now meets the criteria of a SUSAR or reportable device effect. Save all submitted forms into the "Indemnity" folder using the same format name used in ReDA and adding f-u (<u>indicating follow-up</u>). Repeat this process with all follow up information until all events are closed. The date of the event and title remain unchanged - the follow up data should be added to the comments field.
For SUSAR reporting		
9.	GCP & Governance Manager or delegated Clinical trial monitor	Process and log SUSARs as per UK regulatory guidance. Review all valid SUSARs as soon as possible. Event should be processed internally by JRMO as above. Establish Day 0 (as per SOP 26a Associated Document 1) and notify all involved. Log the SUSAR within the Queen Mary and Barts Health ICSR account as per current MHRA guidance and timelines. Any SUSAR occurring in the UK for which the outcome is fatal or life-threatening should be logged within 7 calendar days after the sponsor becomes aware of the event. Non-fatal or non-life-threatening events should be submitted within 15 calendar days after the sponsor becomes aware of the event. Any additional information should be submitted within 8 days of logging the first report. Reports of SUSARs in double-blind studies should be unblinded prior to submission. Procedures related to un-blinding for SUSAR report purposes can be found in study specific SOPs. Events for participants on placebo for blinded studies will not be reported to MHRA however they will be processed and communicated to the trial team as a SUSAR to maintain the blind. Once logged, download the submission PDF, and send it to the Study Coordinator. Do not include CI or blinded staff in any SUSAR correspondence
10.	CI	SAEs related to a NIMP SAEs related to a nIMP should be identified and, if unexpected, reported to the Sponsor who will notify MHRA/regulatory authority, especially if the nIMP is unauthorized.

11.	CI	CI notifies the locations of SUSARs. As sponsor, Bart Health/Queen Mary delegates to the CI responsibility for notifying all locations (Investigators) of SUSARs It is normally the responsibility of the National Coordinating Centres to report SUSARs to the relevant regulatory authorities in their country of origin as per their regulations.
For Clinical Investigations of a Medical Device		
12.	Device Manufacturer or GCP & Governance Manager	Notify the MHRA of reportable safety events occurring on Clinical Investigations of Medical Devices. The device manufacturer should normally be delegated responsibility for reporting events to the MHRA (via the Quarterly Safety Report). The manufacturer may report the event according to their own procedures but must comply with the statutory reporting requirements and must forward a copy of the event report and all correspondence to the JRMO in a timely manner. Where the sponsor retains responsibility for event reporting to the MHRA, this will be completed by the JRMO GCP team. Events that must be reported to the MHRA are: • All SADEs including USADEs • All SAEs that could be related to a comparator or to the investigation procedure. • All device deficiencies that could have led to a SADE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate. Review all valid safety reports as soon as possible after receipt. Establish Day 0 and notify all involved. Ensure that both the Investigator and CI's assessment of the event correspond. If not, discuss with the CI and, if needed, seek independent advice. Report the event as per current MHRA guidance without delay (see MHRA main website for web address). Any interpretation of working should be checked with the CI prior to submission of the report. Events in double-blind Clinical Investigations should be unblinded prior to submission. Procedures related to un-blinding safety reporting purposes can be found in study specific SOPs. Once submitted, save a copy of the report, and send it to the CI, Study Coordinator and the local JRMO Clinical Trial Monitor/Clinical Trial Facilitator for logging at local level. Updates to reportable events must be managed in the same way and in the same timeline as new event reports. In multi-national studies, all events must be reported to the MHRA regardless of the country they occur in. The event may need to be reported to the competent authorities in other countries according to national laws.

		This activity may be delegated to the device manufacturer or to NCC in each country.
13.	CI	Periodically review all recorded AEs and device deficiencies for device trials. Review all adverse events recorded in the case report form (CRF) and confirm agreement or disagreement with the locations assessment of seriousness, relatedness and whether the event is expected. Review all device deficiencies recorded in the case report form and confirm agreement or disagreement with the locations assessment of whether the device deficiency could have led to a SADE. Complete and document the periodic review in accordance with the CIP or other essential documents. The periodic review should take place at least quarterly. In the event that the CI disagrees with the location assessment, they should notify the JRMO. In some circumstances this activity may be delegated to the device manufacturer. If this is the case the contract will detail those delegations, and which SOPs are being followed.
14.	Medical Assessor	Assess received SAE and device deficiency reports All received reports of SAEs and device deficiencies that could have caused SADEs must be reviewed within 72 hours of receipt. The device manufacturer should normally be delegated the responsibility of being medical assessor and may do so according to their own procedures. The device manufacturer must communicate its assessment to the JRMO within 72 hours. Where the sponsor is responsible for assessing received reports, the CI or a suitable medical delegate will be the medical assessor. The medical assessor must review the event and confirm that they agree with the locations assessments concerning the event's seriousness, whether it is related to the device and whether it is an anticipated event. If the medical assessor disagrees with the location, they should notify the JRMO. The JRMO may facilitate discussion between the two parties. However, in the absence of a consensus the event should be processed according to the most severe categorisation. This could lead to events being upgraded and reported to the MHRA. Reports must always represent both assessments.
15.	CI	Notify all locations of all SAEs that have been reported to the sponsor (multi-centre Clinical Investigations only). The process for notifying should be described in the CIP or in another essential document e.g., a study specific safety reporting procedure.
16.	CI	Ensure all relevant committees are provided with all relevant safety information. The process and timing for providing safety information should be described in the CIP or the committee's charter.
17.	Medical Assessor	Assess SADEs and device deficiencies that could have led to SADEs to and determine whether the risk analysis needs to be updated and whether corrective and preventative action is required.

		Where changes to the risk analysis or CIP are required, the sponsor should be notified immediately. A substantial modification must be made to implement the change.
18.	CI	Ensure conditions of MHRA approval is adhered to It is the CI responsibility to ensure the device manufacturer or delegate is adhering to conditions in the initial MHRA approval letter (for example; quarterly safety reporting, deviations reporting, device deficiencies, etc.)
All regulated studies (CTIMP/ATIMP and CIMD)		
Medical assessment of reportable safety events		
19.	CI/Medical Assessor	Assess all reportable events and pregnancies within 72 hours of receipt (note this includes follow up reports). Acting as the sponsor's medical assessor, the CI or appropriate delegate must review all SAEs within 72 hours. The CI must assess the event to determine that it does meet the definition of an SAE, and that the event and narrative are clear and provide sufficient information. The CI's assessment also includes an assessment of: • Seriousness: the final assessment is completed by the Investigator (or delegate). Should a difference of opinion arise the CI and Investigator must discuss the event, but the Investigator at location will make the final decision. • Relatedness: if the CI disagrees with the Investigators assessment, the opinion and explanation of both the CI and Investigator should be provided on the report. However, the Investigators assessment of relatedness will be used to define the event. • Expectedness: decision must be made purely on the content of the RSI in place at the time of the event and should not take into account other factors should as study population or participant history. This applies to all IMPs and investigational devices used in the study. Where the location is asked to make this assessment, please note the final assessment is completed by the CI. This review should be document on the SAE form where possible or can be clearly documented in an email. This assessment should be filed in the TMF.
20.	Clinical Trial Monitor/ Clinical Trial Facilitator	Ensure the JRMO does not process non-reportable events. The following events are normally not reportable as defined in this SOP - CTIMPS: AEs which are not serious and are not an AESI as defined in the protocol. Clinical Investigations: AEs which are not serious and are not AESI. Device Deficiencies have been assessed as not having led to a SADE. Interventional and research sponsored studies: Any event other than unexpected, serious adverse reactions (SAR).

		Hosted studies: All events. Upon receiving a non-reportable event, notify the reporter that the event is not reportable following JRMO procedures. Save the correspondence in indemnity.
21.	CI	Clinical Investigations only: document periodic reviews of all AEs In Clinical Investigations of Medical Devices, the CI must also document a periodic review of all adverse events via Quarterly Safety Report and device deficiencies recorded in the study case report forms.
Medical assessment of pregnancies		
22.	CI	CI must include pregnancy reporting and follow-up procedures in the protocol/CIP. The CI must ensure that the protocol/CIP clearly outlines the procedures that must be followed should a study participant or their spouse become pregnant whilst taking the IMP or using the investigational device during the study period. If pregnancy reporting is felt not to be required, this must be clearly justified in the protocol/ CIP. The sponsor's pregnancy form (see SOP 26a Associated Document 3) must be used when the CI is notified of a pregnancy. Study-specific additions to the pregnancy form may be requested in writing to the JRMO but no fields may be removed from the pregnancy form. The CI must ensure systems are in place at all locations to report pregnancies to the sponsor within 24-hours of becoming aware of the event of a pregnancy, and that all pregnancies are followed to outcome. The length of follow-up post birth must be assessed by the CI using information (IB/ SmPC) and described clearly in the protocol/CIP. Pregnancy follow-up can be through a coordinating centre or the central research team, as appropriate to the care of the participant.
23.	GCP Team	Obtain independent medical advice for any pregnancy reports received When receiving a pregnancy report, the GCP team will request medical review and advice on length of follow up needed from an appropriately qualified person as identified by the Clinical Director for Research & Development.
24.	Clinical Trial Monitor	Log any pregnancy in ReDA as per the instructions in associated document 3.
25.	Clinical Director for Research & Development or delegated other	Arrange for a member of the obstetric department to review any reports of pregnancies that are received by the JRMO. Provide independent medical expertise to the GCP team. Expertise may include, but is not limited to, classifying 'normal' or 'abnormal' birth, length of follow up needed and whether the participant can remain on the study.

26.	GCP Team	Ensure that the CI and study team are aware of and follows the advice. Log all information and documentation within ReDA and study files.
Implement Urgent Safety Measures (USM) (Not applicable for Clinical Investigations)		
27.	Sponsor and CI	Implement USM immediately, inform the MHRA & Research Ethics Committee within 7 days of the urgent safety measure with a modification. The sponsor and investigators may implement urgent safety measures to protect clinical trial participants from any immediate hazard to their health and safety; the measures must be taken immediately. See JRMO SOP 17a Amendments for Halted Studies for the USM Procedure.
Reconciliation, Ongoing oversight, and annual review		
28.	CI/Medical Assessor	Once the study is active, review the RSI at intervals agreed with GCP manager at set up at a minimum yearly in line with DSUR creation (CTIMPs) or QSR (Clinical Investigations). An SOP should be created to document and log this process.
29.	Clinical Trial Monitor	Every 6 months and following every onsite monitoring event perform study specific reconciliation for all live MHRA regulated studies. Every 6 months (or on receipt of SMR) generate a study specific SAE Log on ReDA and compare it to the coordinating team's SAE Log sent with the quarterly monitoring report/ acquired during monitoring visits or requested from the study team. Perform reconciliation to ensure accuracy and that all documents appropriately stored. Confirm completion to trial coordinator and in Edge. Save both logs and all related correspondence in the "Indemnity" folder and file in the JRMO sponsor's files. As the Study nears its end- ensure the CI and study team are aware of the need to close all SAEs or confirm that the SAE is open ongoing at end of study.
30.	Clinical Trial Monitor	Prepare reports for the SOG meeting In preparation for the sponsor oversight group meeting, run report from ReDA as requested by the GCP & Governance managers, likely to include but not limited to: The number of SAEs, Serious Adverse Reactions and SUSARs or SAEs, SADEs and USADEs for all sponsored MHRA-regulated studies within reporting period. Number of device deficiencies that could have led to SADEs in all sponsored Clinical Investigations of Medical Devices within the reporting period. To identify 'on time' and 'late' reported SAEs and other safety events. All late reported SAEs and SUSARs/ reportable device events for that quarter are to be highlighted and documented at the pre-sog meeting. Any evident trends will be discussed at this meeting and escalated to the JRMO QA manager as a non-compliance Provide figures to the Clinical Trial Facilitator to compile meeting papers.

31.	SOG members	Review safety information as per group remit. Action, as necessary.
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Change control

This section outlines changes from version **4.0** to version **5.0**

Section changed	Summary and description of changes
Throughout	General administrative changes throughout
Page 1	Merger of Purpose and Scope
Section 3	Streamlining of instructions for Safety Reporting Systems
Section 11	Update to instructions for CI regarding SUSAR notification
Throughout	Requirement changes of reporting to the REC
Section 27	Extension to 7 calendar days for USM reporting to relevant regulatory bodies
Annual review	Removal of requirement for Annual Progress Reports
Associated Document 1	RSI guidance updated in line with ICH E6 (R3)

List of associated documents

Document ref.	Document name
Associated Document 1	RSI Guidance
Associated Document 2	ReDA instructions to log safety events

List of templates

Document ref.	Document name
Template 1	RSI log template
Template 2	Template AESI Form