Standard Operating Procedure (SOP) for:			
Pharmacovigilance (Process for the JRMO)			
SOP Number:	**26c**	Version Number:	**2.0**
Effective Date:	**25th June 2018**	Review Date:	**25th June 2020**

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Purpose:

This standard operating procedure (SOP) outlines the actions and responsibilities of the joint research management office (JRMO) regarding safety reporting.

This SOP will identify and standardise the process for receiving, logging and acknowledging serious adverse events (SAEs), serious adverse reactions (SARs), suspected unexpected serious adverse reactions (SUSARs), adverse events of special interest (AESI) and pregnancies for projects sponsored by Barts Health NHS Trust (BH) or Queen Mary University London (QMUL).

Scope:

This SOP is relevant to the JRMO staff and associated staff named within this SOP only.

Please note:

The JRMO research database application (ReDA) is used to collect and record pharmacovigilance (PV) 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 Chief Investigator (CI).

Abbreviations:

AESI	Adverse Event of Special Interest
ATIMP	Advanced Therapy Investigational Medicinal Product
BH	Barts Health NHS Trust
CI	Chief Investigator
CTF	Clinical Trial Facilitator
CTIMP	Clinical Trial of an Investigational Medicinal Product

GCP	Good Clinical Practice
HRA	Health Research Authority
JRMO	Joint Research Management Office
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PV	Pharmacovigilance
QA	Quality Assurance
QMUL	Queen Mary University of London
REC	Research Ethics Committee
ReDA	Research Database Application
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

Definitions:

See Appendix A for study definitions.

Relevant SOPs:

- SOP 26a Pharmacovigilance reporting for MHRA-regulated trials
- SOP 26b Pharmacovigilance and safety reporting for sponsored interventional and research studies

SOP Text:

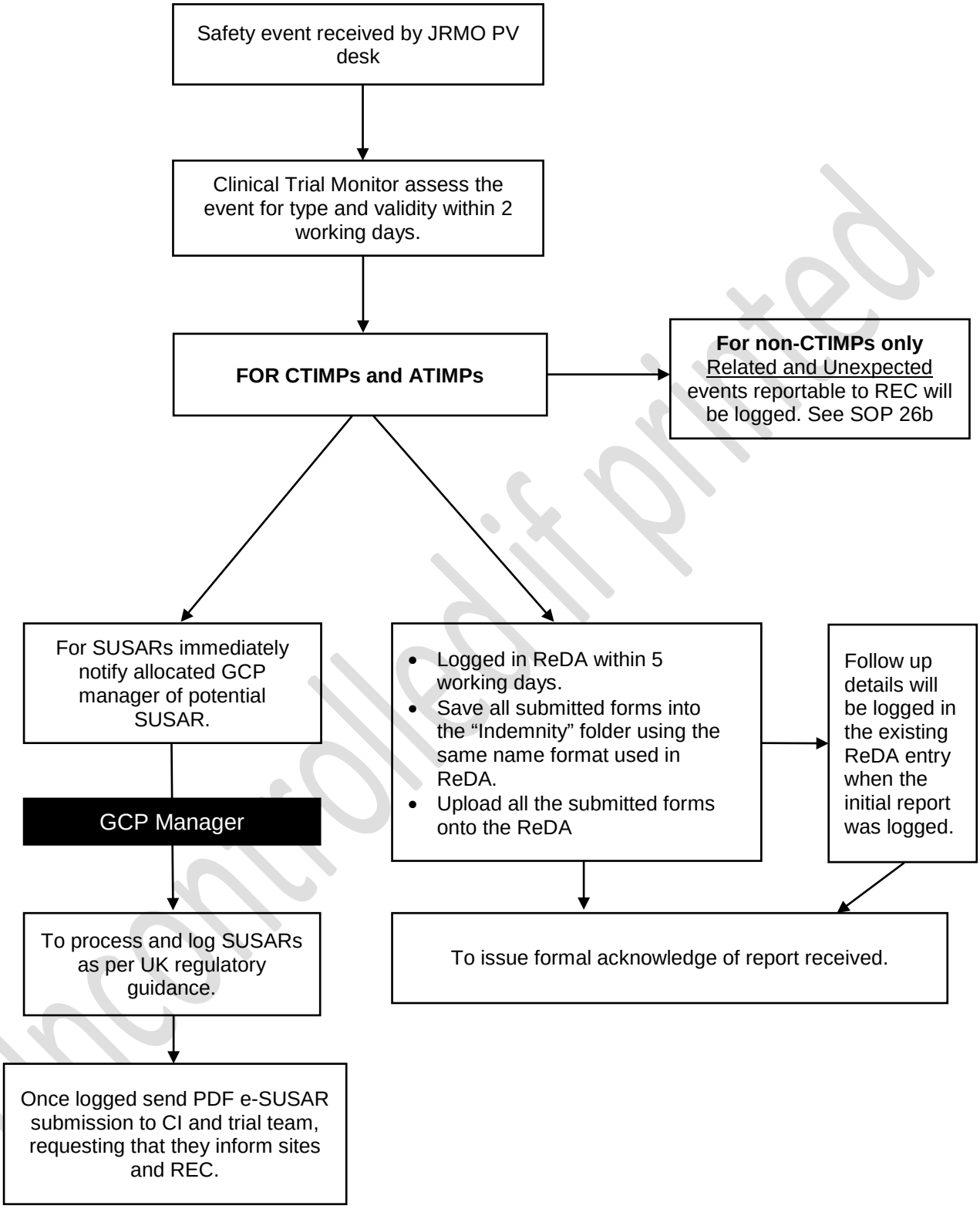
	Responsibility	Activity
1.	R&D Governance Operations Manager	**<u>Ensure a suitable database is available to log and manage safety events on behalf of QMUL and BH sponsored studies.</u>**
2.	GCP & Governance Manager	**<u>Assign a JRMO Clinical Trial Monitor to manage the PV desk for each study.</u>** Ensure the Clinical Trial Monitor is appropriately trained prior to PV assignment and adequately supported throughout. Ensure the PV desk is appropriately supported, managed and covered at all times. Ensure allocated staff have access to the PV safety email inbox.
3.	Clinical Trial Monitor	**1. Check the PV desk for new correspondence at least every working day.** All new events should be assessed within two working days: • To establish if the JRMO's procedures require these to be logged. o The JRMO will only log AESI, SAES, SUSAR's and pregnancies for clinical trials of an investigational medicinal product (CTIMPs), clinical trials of advanced therapy investigational medicinal products (ATIMPs) and clinical investigations.

		o For non-CTIMPs, only <u>related and unexpected</u> events reportable to research ethics committee (REC) will be logged. • For type of event (Pregnancy/SAE/SUSAR). • For completeness/validity of submission. **2. For SUSARs, immediately notify one of the GCP & Governance Managers (or, if absent, the QA Manager).** **3. Log the event within ReDA's Post Approval tab using the above principles** (see associated document 1). **All events must be logged within 5 working days.** **4. All submitted forms must be saved into the "Indemnity" folder using the same format name used in ReDA:** Sub 'Study patient number/ID', SAE 'Event name', JRMO 'date SAE received by JRMO/dd-mm-yy' Example: Sub R055, SAE Portal Vein Thrombosis, JRMO 21-1-16 **5. Upload all submitted forms onto the 'Safety' section on the 'Documents' tab in ReDA.** Ensure SAE files are labelled correctly (see associated document 1). **6. Issue formal acknowledgement of the event on the day the event has been assessed for validity.** Acknowledgement should be sent to the sender and Trial Coordinator, stating the name of the logged SAE and whether there is any missing information or signatures that have still to be received. **7. Follow up events.** Follow up details will be logged in the existing ReDA entry where the initial report was logged. **8. 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>**:** **When notified of a pending end of trial, ensure all events are reconciled/closed.** **9. Ensure that all safety events correspondence is filed within the "Indemnity" folder.** **Every other quarter generate a study specific SAE Log on ReDA and compare it to the coordinating team's SAE Log sent with the quarterly monitoring report. Save both logs in the "Indemnity" folder and file in the JRMO sponsor's files.**
4.	GCP & Governance Manager	**<u>Process and log SUSARs as per UK regulatory guidance.</u>** Review all valid SUSARs as notified by Clinical Trial Monitor. Establish Day 0 and notify all involved. Ensure that both the PI's and CI's assessment of the SUSAR correspond. If not, discuss with the CI and, if needed, seek independent advice as per sections 6 and 7. Log the SUSAR within the QMUL and BH e-SUSAR account as per current Medicines and Healthcare products Regulatory Agency (MHRA) guidance and within UK regulatory and Health Research Authority (HRA) timelines (see MHRA main website for web address).

		Any SUSAR occurring in the UK which is fatal or life-threatening should be logged **within 7 days** after the sponsor becomes aware of the event. Non-fatal or non-life threatening events should be logged **within 15 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 trials should be unblinded prior to submission. Procedures related to un-blinding for SUSAR report purposes can be found in study specific SOPs. Any interpretation of wording on SUSAR reports should be checked with CI prior to eSUSAR submission. Once logged, download the submission PDF and send it to the CI, Trial Coordinator and the local JRMO Clinical Trial Monitor for logging at local level.
Medical assessment of SAEs/SARs/SUSARs/AESI & pregnancy		
5.	Sponsor Oversight Group / CI	**<u>Ensure the CI fulfils their role as CI and medical assessor. The CI is delegated by the sponsor to be the PV medical assessor.</u>** The CI must ensure sites are aware of the requirement to report SAEs, SARs, SUSARs, AESI and pregnancies to the JRMO. On the rare occasion that the CI fails to comply with PV reporting timelines or provide adequate CI oversight, as outlined in *SOP 26a*, the sponsor will escalate this in accordance with their escalation policy, commencing with the sponsor oversight group in JRMO. Unless otherwise formally agreed by the sponsor and a delegated body, the sponsor is responsible for ensuring that all relevant information about 'UK-relevant SUSARs are reported to the competent authority (MHRA). (See Appendix A for the MHRA's definition of 'UK-relevant').
6.	GCP Team / Clinical Director for Research & Development	**<u>Seek independent review in cases of dispute between the CI and PI when assessing an SAE.</u>** Should such a dispute arise, the GCP team will contact the Clinical Director for Research & Development for clinical expertise and resolution. The Clinical Director is ultimately responsible for making a final decision on behalf of the sponsor.
Medical assessment of pregnancies reported in a CTIMP/ATIMP		
7.	GCP Team	**<u>Obtain independent medical advice for any pregnancy reports received.</u>** 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.
8.	Clinical Trial Monitor	**<u>Log any pregnancy in ReDA</u>** as per the instructions in associated document 1.
9.	Clinical Director for Research & Development	**<u>Arrange for a member of the obstetric department to review any reports of pregnancies that are received by the JRMO.</u>** 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.

10.	GCP Team	**<u>Ensure that the CI and study team are aware of and heeds the advice.</u>** Log all information and documentation within ReDA and study files.
Annual reporting		
11.	GCP & Governance Manager	**<u>Review BH and QMUL sponsored CTIMPs annual progress reports (APRs) and development safety update reports (DSURs).</u>** This review should include ensuring that current templates are used, that all sections are complete and that all information is correct (to the sponsor's knowledge) e.g. all SUSARs are listed. Inform the QA Manager if submissions are late.
12.	QA manager	**<u>Log all late CTIMP submissions on the non-compliance log.</u>** Work with the Clinical Trial Facilitator to compile quarterly figures for sponsor oversight group meetings (as per Section 14) including any lateness that needs to be escalated to the sponsor oversight group.
13.	Assigned Clinical Trial Monitor	**<u>Ensure reminders are set up and actioned (this includes appropriate escalation) within ReDA</u>** as per associated document 2. Individual event reminders must not be switched off until final version and submission evidence is received. Ensure draft copies of annual reports, GCP & Governance Manager's approval, final version and evidence of submission are saved.
Sponsor oversight group		
14.	Clinical Trial Monitor	**<u>In preparation for the sponsor oversight group meeting, run two reports</u>:** 1) Number of SAEs, SARs and SUSARs for all sponsored MHRA-regulated trials within reporting period. 2) To identify 'on time' and 'late' reported SAEs and SUSARs. Assist the Clinical Trial Facilitator in collating annual reports – due, completed and overdue. Provide figures to the Clinical Trial Facilitator to compile meeting papers.
15.	Sponsor Oversight Group members	**<u>Review safety information as per group remit.</u>** Action as necessary.

Summary of the pharmacovigilance process for the JRMO



Change control

This section outlines changes from version **1.0** to version **2.0**

Section changed	Summary and description of changes
Section 6	Sections 6 and 7 combined into one. All subsequent sections renumbered.
Section 14	Change in responsibility of who is responsible for sponsor oversight group meeting PV reports.
All	Faxes no longer accepted.
All	General administrative changes.

List of appendices

Appendix ref.	Appendix name
Appendix A	Definitions

List of associated documents

Document ref.	Document name
1	ReDA instructions to log safety events
2	ReDA template email for APR & DSUR reminders

Appendix A

Definitions:

Investigational Medicinal Product (IMP): An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial including products already with a marketing authorisation.

Non-Investigational Medicinal Product (NIMP): Products that are not the object of investigation (i.e. other than the tested product, placebo or active comparator) that may be supplied to subjects participating in a trial and used in accordance with the protocol. For instance, some clinical trial protocols require the use of medicinal products such as support or rescue/escape medication for preventative, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. These medicinal products do not fall within the definition of an IMP and are called NIMPs.

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Adverse Event of Special Interest (AESI): An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g. regulators) might also be warranted. (Based on CIOMS VI)

Serious Adverse Event (SAE): Any adverse event or adverse reaction that:

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect.

Note: Some medical events may jeopardize the subject or may require an intervention to prevent one of the above characteristics or consequences. These should also be considered as 'serious' in accordance with the definition.

Serious Adverse Reaction (SAR): Any adverse reaction that is classed as serious in nature and where there is evidence to suggest a causal relationship between the drug and the adverse event.

Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse reaction that is classed as serious in nature and which is not consistent with the information about the medicinal product in question. In the case of a licensed product, the summary of product characteristics (SmPC) for that product. In the case of any other investigational medicinal product, the Investigator's Brochure (IB) relating to the trial in question. Note: to fulfill the definition of SUSAR there must be suspicion of a causal relationship between the event and the IMP.

UK relevant SUSARS: The MHRA's definition of 'UK relevant' includes:

- SUSARs originating in the UK.
- SUSARs originating outside the UK where the sponsor has an ongoing trial in the UK involving the same medicinal product.

Day '0': The day the Chief Investigator first receives a written SAE report (usually by email), which has been medically assessed by the site.

Urgent Safety Measures: An urgent safety measure is a procedure not defined by the protocol that is put in place prior to authorisation by the sponsor, MHRA, REC and sponsor in order to protect clinical trial subjects from any immediate hazard to their health and safety. During the course of a clinical trial involving an IMP, new safety information in the form of a SAE or information received from an external source may necessitate an immediate change in the study procedures or a temporary halt to the study in order to protect clinical trial subjects from any immediate hazard to their health and safety. If time does not allow for an amendment to be authorised by the sponsor, MHRA, and REC, this change in procedure can be implemented as an urgent safety measure by the Investigator, in accordance with the process put in place by the MHRA.

Code Break/Unblinding: Code break involves unblinding a participant so that the treatment allocation is made known. This can be single (just to research team) or double (to research team and participant; be cautious not to unblind others involved in the study)