Standard Operating Procedures (SOP) for:			
For researchers: Pharmacovigilance and Safety Reporting for Sponsored CTIMPs/ATMP			
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Background

Under the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and all subsequent amendments, sponsors of clinical trials of medicinal products have legal requirements for recording and reporting serious adverse events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs). Of particular importance is th e assessment of any event for causality and expectedness. Under the Research Governance Framework 2005, researchers have a responsibility to record any adverse drug reaction or other adverse events (AEs). It is vital that this SOP is followed as failure to record and report SAEs/SUSARs or deal with them adequately can have the potential to jeopardise the safety and well-being of trial subjects.

Purpose and Objective

To identify and standardise the process for recording, managing and reporting Adverse Events (AEs), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) and Urgent Safety Measures (USM). This Standard Operating Procedure (SOP) also describes the procedure for safety reference information (RSI) updates, annual reports to regulators including Data Safety Update Reports (DSURs) and Annual Progress Reports (APRs) and the management of pregnancy.

This SOP also outlines the Investigator's responsibilities to ensure oversight and management of pharmacovigilance of Barts Health NHS Trust (BH) and Queen Mary University of London (QMUL) sponsored CTIMPs.

Scope

This SOP covers procedures for Barts Health NHS Trust (BH) and Queen Mary University of London (QMUL) sponsored Clinical Trials of Investigational Medicinal Products (CTIMPs) and Advanced Therapies of Medicinal Products (ATMP).

Reporting mechanisms for SAEs in CTIMPs are determined by the trial sponsor. The Principal Investigator (PI) informs the sponsor of SAEs that occur in all trial participants at their site in accordance with the sponsor's pharmacovigilance SOP and/or the process outlined in the protocol.

For all studies sponsored by external organizations i.e. other NHS Trusts, universities other than QMUL, or commercial companies, the sponsor's pharmacovigilance procedure must be followed. Sections 12 & 13 of this SOP covers the reporting requirements for externally sponsored studies, however the general principles outlined in this SOP can be applied to all studies.

Responsibilities:

For study specific arrangements please see the study specific Conditions of sponsorship agreement.

In general terms:

For multi-site trials, the Chief Investigator (CI) has overall responsibility for all the sites including pharmacovigilance and safety reporting.

The CI is delegated by the sponsor to be the pharmacovigilance medical assessor.

The CI delegates responsibility for pharmacovigilance to the Principal Investigator (PI) of each site. There is one PI at each research site. In single-site trials, the CI and PI is normally the same person and is responsible for the site's pharmacovigilance. The PI is responsible for informing the CI of all SAEs/SUSARs that occur at their site in accordance to the guidance below. On the rare occasion that the CI fails to comply with pharmacovigilance reporting timelines or provide adequate CI oversight as outlined in this SOP, the sponsor will escalate this in accordance with their escalation policy.

Unless otherwise formally agreed by the sponsor and delegated, the sponsor is responsible for ensuring that all relevant information about a SUSAR which occurs during the course of a clinical trial in the United Kingdom, or that are 'UK-relevant' are reported to the Competent Authority (MHRA).

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

Abbreviations:	
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATMP	Advanced Therapy of Medicinal Product
BH	Bart's Health NHS Trust
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTSU	Clinical Trials Systems Unit
eCRF	Electronic Case Report Form
DMP	Database Management Plan
GCP	Good Clinical Practice
JRMO	Joint Research Management Office
MHRA	Medicines and Healthcare products Regulatory Agency
Non-CTIMP	Clinical Trial with no investigational medicinal product i.e. non-drug trial
PI	Principal Investigator
QMUL	Queen Mary University of London
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
VHP	Voluntary Harmonisation Procedure

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.

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

- Results in death
- Is life threatening
- Requires hospitalization or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect.
- Requires intervention to prevent permanent impairment or damage

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:

a. In the case of a licensed product, the summary of product characteristics (SmPC) for that product.
b. 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.

Day '0': The day the Chief Investigator first receives a written SAE report (by fax or 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 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 Serious Adverse Event 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 Research Ethics Committee (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, and as detailed in this SOP.

Code break: 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).

Investigator's Brochure (IB): The IB is a comprehensive document that summarises the known information about an IMP. It is a compilation of the clinical and non-clinical data on the investigational product(s) which is relevant to the trial. According to ICH GCP the purpose of the IB "to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures." The IB is of critical importance throughout the drug development process and is updated with new information as it becomes available. Once the drug has a marketing authorisation in any EU member state, the Summary of Product Characteristics (SmPC) is accepted as an adequate replacement for the IB where the drug is used

according to the terms of this authorisation.

Reference Safety Information (RSI): The RSI documents are used to assess the expectedness of SAEs for clinical trials. In clinical trials the RSI is documented in the Summary of Product Characteristics (SmPC), or the investigator brochure (IB) and the protocol.

Summary of Product Characteristics (SmPC): The SmPC is a document that relates to a marketed medicinal product. It contains a description of the product's properties and the conditions attached to its use. This document is important as it describes all known expected adverse reactions. The holder of the marketing authorization of the medicinal product will routinely update the SmPC based on receipt of new information.

Related SOPs

SOP 26b Safety reporting for non-CTIMPs: For guidance on safety reporting for Barts Health NHS Trust (BH) and Queen Mary University of London (QMUL) sponsored Non-CTIMPs.
SOP 47 Trial Committees
SOP 17a Amendment - process for JRMO
SOP 17c Amendment - Process for researchers
SOP 19 Project closure: guidance for JRMO staff

SOP Text

	Responsibility	Activity
Study and protocol design.		
1.	Chief investigator	**When designing the study, ensure that the Research Safety Information (RSI) is clearly defined in the protocol and, once the trial is active review the RSI every year.** The CI must ensure that the protocol clearly outlines the pharmacovigilance procedures for their trials. Chief Investigators who fail to regularly review the RSI will be escalated by the Sponsor oversight group in accordance with their escalation policy. International trials: New versions of SmPCs or IBs must be approved by the sponsor before submission for regulatory approval, and, if the trial 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 (see point 17).
2.	Chief investigator	**Ensure Systems in place to Report SAEs within 24-hours.** The sponsor SAE form (See Associated Document 2) must be used when reporting SAEs. Requests to amend the sponsor SAE form (See Associated Document 2) with trial specific additions must be made in writing to the JRMO. No fields may be removed/omitted from the sponsor's SAE Form. The CI must ensure that there are systems in place at all sites to report SAEs and SUSARs to the sponsor within 24 hours of the site becoming aware of the event. The mechanism to report to the sponsor within 24-hours may be through a coordinating centre or the research team. CI should design and implement a study specific system to ensure that, unless otherwise delegated, the Sponsor receives SAE and SUSAR reports within 24 hours of the site becoming aware of the event, and the CI acting as Medical assessor for the sponsor (or delegate) reviews events in a timely manner.
RECORDING & REPORTING OF EVENTS for BH and QMUL Sponsored studies		
3.	Principal Investigator	**Record AEs in patients' notes and assess whether AEs are serious (i.e. SAEs) and whether they need to be reported to the sponsor.** If an Adverse Event (AE) occurs during a research project the PI must follow the flowchart in Associated Document 1.

		Each event must be identified and reported separately. Care must be taken to avoid reporting/recoding the symptoms of the event, rather than the event itself. The Principal Investigator (PI) or the medically qualified delegate for the study site must assess the AE to establish if it must be classified as an SAE (Serious Adverse Event). This assessment must occur within a timely manner to allow the event to be reported within 24 hours if necessary. A serious adverse event (SAE) in human drug trials is defined as any untoward medical occurrence that: 1.results in death 2.is life-threatening 3.requires inpatient hospitalisation or causes prolongation of existing hospitalisation 4.results in persistent or significant disability/incapacity 5.is a congenital anomaly/birth defect, or 6.requires intervention to prevent permanent impairment or damage If the AE **is** defined as SERIOUS as per the criteria above, **proceed to section 4**. If the AE is **not** defined as SERIOUS, the AE is recorded in the case report form (CRF) and the participant is followed up by the research team until resolution. The AE must be documented in the participant's medical notes (paper or electronic medical notes as appropriate). For some trials the IMP manufacturer/funder may identify AEs of special interest (AESI). An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the IMP or trial, for which ongoing monitoring and rapid communication by the investigator to the sponsor/IMP manufacturer maybe 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. **Please see section 10** for more details.
4.	Principal Investigator	**Report the SAE to the sponsor or delegate as defined in the protocol.** Details of the SAE must be recorded in the participant's source data, and the participant followed up by the research team to resolution of the event. The PI must report all SAEs to the sponsor according to the protocol and any trial specific SOPs. The sponsor SAE form (See Associated Document 2) **must be used.** An SAE form should be completed for each SAE that requires reporting. **The PI's team must complete the BH/QM SAE reporting form**, Associated Document 2 (BH/QMUL SAE template form). **Once completed/partially completed, the SAE form must be signed by the PI or appropriate delegated medically qualified person at the site.** SAEs which have not been signed by PI or delegated medical representative will not be accepted by the sponsor and will be returned to the PI to be completed. A scanned signed copy should be emailed to: Research.Safety@bartshealth.nhs.uk Alternatively if scanning facilities are not available at the site the SAE form must be faxed to the JRMO fax number +44 207 882 7276, along with an email notifying the JRMO Research.Safety@bartshealth.nhs.uk so that they can ensure receipt of the

		SAE. The SAE **must** be reported to the sponsor within 24 hours of the site becoming aware of the event. If the trial is NOT SPONSORED by BH/QM, please note that the sponsor's SAE form needs to be sent to the sponsor only and not the JRMO. **Report the SAE to Sponsor.**
5.	Principal Investigator	**Assess whether an Adverse Event is related to the trial's IMP or NIMP to establish whether or not it is a Serious Adverse Reaction (SAR).** Prior to submitting the SAE the PI/medically qualified individual treating/responsible for the treatment of the participant must make an assessment of relatedness of the event to the trial IMPs and NIMPs. Following this assessment the research team sends the report to the sponsor as per protocol procedures. If the SAE is assessed as **not** being a reaction to the medicinal product, **proceed to section 4**. If the SAE is classified as being **possibly** a reaction to the medicinal product, the SAE is classified as a SAR (Serious Adverse Reaction). **Proceed to section 6**.
6.	Principal Investigator	**Assess whether a Serious Adverse Reaction (SAR) is expected.** Once established that it is a SAR, the PI must assess the expectedness (whether the reaction to the IMP or NIMP was expected). To make the expectedness assessment the PI must review the trial specific Reference Safety Information (RSI) together with the protocol. The RSI is listed in the Investigators Brochure (IB) or the Summary of Product Characteristics (SmPC). If the SAR is **expected** in the IB/SmPC and protocol, **proceed to section 8** for reporting process. If the SAR is **unexpected**, **proceed to section 7.**
7.	Principal Investigator	**Assess whether the Serious Adverse Reaction is unexpected, i.e. is this a SUSAR?** If the PI has assessed that the SAR as unexpected it should be classified as a SUSAR (Suspected Unexpected Serious Adverse Reaction). A SUSAR is an SAE which is suspected to be a reaction to the medicinal product and is **UNEXPECTED** i.e. it has not been seen before in the RSI. For SUSAR reporting process, **proceed to section 9.**
8.	Principal Investigator	**Report the expected SAR to Sponsor.** An SAE form is completed for each SAR that requires reporting and submitted to the JRMO as **per section 2**. The SAR must be recorded in the participant's source data and the participant followed up to event resolution by the research team.
9.	Principal Investigator	**Report unexpected SARs (SUSAR) to the Sponsor within 24 hours.** **Unexpected SAR or SUSAR reporting process.** SARs that are UNEXPECTED and therefore fulfil the criteria of a SUSAR require "immediate" reporting to the sponsor. The PI reports the SUSAR form (using the same form as SAEs). The form must be signed by the PI or appropriate delegated medically qualified person at the site. A scanned signed copy should be emailed to: Research.Safety@bartshealth.nhs.uk Alternatively if scanning facilities are not available at the site the SAE form must be faxed to the JRMO fax number is: +44 207 882 7276, along with an email notifying the JRMO Research.Safety@bartshealth.nhs.uk so that they can ensure receipt of the SUSAR. The sponsor will acknowledge receipt of the SUSAR in writing to the PI or coordinating team (depending on submitting party and agreements). If the PI does not receive an acknowledgement of receipt the PI must contact the sponsor and request a written acknowledgment.

		If follow up information to an SAE/SAR becomes available, the PI or delegate should re assess the event. If this reassessment indicates that the event has become a SUSAR the PI should submit it to the sponsor as per the instructions above. Should follow-up information for a SUSAR be received by the sponsor before the reportable deadline i.e. it has been downgraded to an SAE/SAR, the event will not be reported to the Competent Authority by the Sponsor. However, the sponsor must be provided with the reasons given for the downgrade by the PI and confirmation that the CI is in agreement.
10.	Principal Investigator	**To inform the Sponsor about Adverse Event of Special Interest (AESI).** If the event is not classed as serious, but is seen as an AESI, the PI must inform the sponsor who will report this to the MHRA following the same timelines as for reporting a SUSAR. AESI may be: 1. An increase in the rate of occurrence of an expected serious adverse event, which is judged to be clinically important 2. Post-study SUSARs that occur after the patient has completed a trial 3.A new event, related to the conduct of the trial or the development of the investigational medicinal product (IMP), that is likely to affect the safety of subjects, such as: • A serious adverse event that could be associated with the trial procedures and which could modify the conduct of the trial; • A significant hazard to the subject's population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease; a major safety finding (for example, carcinogenicity) from a newly completed animal study; • Any anticipated end to a trial or temporary halt for safety reasons where the trial is conducted by the same sponsor with the same IMP in another country; • The conclusions or recommendations of a data monitoring committee, where relevant for the safety of subjects. The MHRA recommends expedited reporting both to MHRA and the REC of any information that materially alters the current risk/benefit assessment of the IMP or merits changes in the way the IMP is administered or the overall conduct of the trial.
11.	Chief Investigator	**CI assesses each SAE, SAR, and SUSAR.** Acting as the sponsor's medical assessor, the CI or appropriate delegate must review all SAEs within 48 hours. The Day 0/Zero for reporting the SUSAR will be the date the follow-up information was received the Chief Investigator. The CI must assess seriousness, relatedness and expectedness. This assessment must be documented and submitted to the JRMO. Please note: The CI CAN UPGRADE AN AE to an SAE or SAE to SAR and SAR to SUSAR **BUT CANNOT DOWNGRADE ANY SAE to AE, SAR to SAE.** Should a difference of opinion arise the CI and PI must discuss the event, but the PI at site will make the final decision. As Medical assessor for the sponsor the CI will make the final decision on expectedness and may override the PI.
12.	GCP team	**To seek independent review in case of dispute between CI and PI when assessing an SAE.** Should a dispute arise between CI and PI when assessing an SAE, the GCP team will contact the Clinical Director for Research and Development for clinical expertise.

13.	Clinical Director for Research and Development	**To provide or arrange independent review to the GCP team in case of dispute between CI and PI when assessing an SAE.** The Clinical Director for Research and Development review will be consider the final decision in order to resolve the dispute.
14.	Chief Investigator	**Ensure Sponsor is able to unblind events where applicable.** When a participant is on a blinded study and they have a SUSAR, their treatment codes must be unblinded for the specific subjects prior to the sponsor submitting the SUSAR report. In this instance, the sponsor and Chief Investigator will follow the study specific un-blinding SOP. Once treatment has been un-blinded the patient will be withdrawn from the Trial. In the case of a SUSAR arising from a comparator drug or study procedure, it must be reported to the sponsor, who is also obliged to report to the MHRA. Events associated with a placebo will usually not satisfy the criteria for an Adverse Reaction and therefore will not be subject to expedited reporting. However, where SUSARs are associated with the placebo, the CI must report to the sponsor who will notify the Competent Authority.
15.	Chief Investigator	**If the SUSAR is arising from a NIMP and this has been assessed as likely to affect the safety of the trial participants, this should be reported to the sponsor who will notify MHRA.** If the SUSAR is definitely attributed to a NIMP and is not considered to be related in any way to an IMP, and is not considered to constitute a hazard to the safety of other trial participants this should be reported to the Sponsor who will assess the need along with the CI to report to the Competent Authority, or whether standard safety reporting should be considered (yellow card scheme). In the case of a SUSAR arising from either: • A suspected interaction between IMP and an NIMP, or • Either an IMP or a NIMP but the PI/CI cannot attribute either one of these The event must be reported to the sponsor who will notify the Competent Authority.
16.	Chief Investigator	**CI notifies the sites and REC of SUSARs.** As sponsor, BH/QMUL delegates to the CI responsibility for : • Informing the appropriate REC of SUSARs that have occurred in the UK* • Notifying all sites (PIs) of SUSARs International Trials *NB. It is not a requirement to notify the UK REC of non-UK SUSARs. It is normally the responsibility of the National Coordinating Centres (NCCs) to report SUSARs to the relevant international RECs in their country of origin. The SAE must be reported to the REC if it relates to the following: • A new event, related to the conduct of the trial or the development of the investigational medicinal product (IMP) that is likely to affect the safety of subjects. • An SAE 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. Expected SARs do not need be reported to the main REC apart from in the following situations: • Single case reports of an expected serious adverse reaction with an unexpected outcome e.g. death

		• An increase in the rate of occurrence of an expected serious adverse reaction which is judged to be clinically important.
Pregnancy within an CTIMP/ATMP		
17.	Chief Investigator	**CI must include pregnancy reporting and follow-up procedures in the protocol.** The CI must ensure that the protocol clearly outlines the procedures should a trial participant and/or spouse become pregnant whilst taking the IMP during the study period. The sponsor's pregnancy form (See Associated Document 5) must be used when the CI is notified of a pregnancy. Trial-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 sites 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 IMP Information (IB/ SmPC) and described clearly in the protocol. Pregnancy follow-up can be through a coordinating centre or the central research team, as appropriate to the care of the participant.
18.	Principal Investigator	**PI notifies Sponsor of all pregnancies and follows them up to conclusion.** Within 24 hours of becoming aware of a participant or spouse pregnancy, the PI/s at site/s is responsible for notifying the sponsor (as per protocol) using the sponsor's SAE form. The PI is responsible for collecting all information and following up the pregnancy to outcome and according to the protocol's specified follow-up period.
19.	GCP team	**Obtain independent medical advice for any pregnancy reports received.** When receiving a pregnancy report, the GCP team will request medical advice to a Professor of Women's Health and Clinical Epidemiology.
20.	Professor of Women's Health and Clinical Epidemiology	**To provide independent medical expertise to the GCP team.** The Professor of Women's Health and Clinical Epidemiology will also arrange for a member of the obstetric department to review any reports of pregnancies that are received by the JRMO.
Annual reports		
21.	Chief Investigator/ Principal Investigator	**CI must submit annual reports to REC and safety reports (DSURs) to MHRA.** As sponsor, BH/QMUL delegates to the CI the responsibility of creating and submitting all annual reports (see below). The CI must create draft reports and submit to the sponsor via research.safety@bartshealth.nhs.uk for review prior to submission to REC or MHRA. Once approved by the JRMO, the reports must be finalised, signed and submitted as appropriate. Evidence of submission must be retained in the Trial Master File (and site files). A copy of the final signed report must be sent to the JRMO for their project file, along with evidence of their submission to regulators and any subsequent acknowledgements. <u>Annual Progress Reports (APR) to be sent to REC.</u> Annual progress reports are submitted to the REC which gave the favourable opinion 12 months after the date on which the favourable opinion was given. CI must submit an APR no later than 30 days after the anniversary of the trial's REC favourable opinion letter. For Clinical Trials of Investigational Medicinal Products (CTIMPS), use the national ethics template report in Associated Document 3, as found on the HRA website.

		Development Safety Update Reports (DSUR) to be sent to the MHRA and to the REC. The CI must submit a DSUR no later than 60-days after the anniversary of the trial's MHRA approval (date on the "Notice of acceptance letter). The DSUR should cover a one year period and no longer. The reporting period ends on the anniversary of the trial's MHRA approval. At the end of the DSUR reporting period the CI must assess the new safety information that has been generated and submit any proposed safety changes to the investigator's brochure as a substantial amendment. This amendment should be supported by the DSUR and approved before the reference safety information (RSI) is changed. The RSI for any investigational medicinal product involved in a clinical trial must stay consistent during each reporting period. The development safety update reports (DSURs) should take into account all new available safety information received during the reporting period. The DSUR should include: • A cover letter listing all EudraCT numbers of trials covered by the DSUR, including any trials approved via the Voluntary Harmonisation Procedure (VHP) process. • An analysis of the subjects' safety in the concerned clinical trial(s) with an appraisal of its ongoing risk/benefit. • A line listing of all suspected serious adverse reactions (including all SUSARs) that occurred in the trial(s), including all SUSARs from third countries. • An aggregate summary tabulation of SUSARs that occurred in the concerned trial(s). Full details of what to include in a DSUR are on the European Commission website. The DSUR needs to be sent by the CI to the MHRA using Associated document 4: Development Safety Update Report template. For full details on how to submit DSURs see the MHRA website. In addition to DSURs and APRs, the adverse reactions/events should be summarised in the final Clinical Study Report (CSR) including those that are considered non-serious, in the form of frequency tables. Further information can be found in SOP 19 Study closure.
Urgent Safety Measures		
22.	Chief Investigator/ Sponsor/ Principal Investigator	**Implement urgent safety measures immediately, seek advice from the MHRA and sponsor before (if possible), inform the MHRA & REC within 3-days of the urgent safety measure with an amendment** The sponsor and Investigators may take appropriate urgent safety measures to protect clinical trial subjects from any immediate hazard to their health and safety (Reg 30). The measures must be taken immediately. The Investigator does not need to wait for Competent Authority approval before implementing urgent safety measures; however, they must inform the MHRA in writing within 3 days. On becoming aware of a potential hazard the CI or delegate must contact the sponsor immediately with the full decision making process information that lead to the implementation of the urgent safety measure. The CI must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (see MHRA website for telephone contact details). If the CI is unable to contact the sponsor or MHRA an Urgent Safety Measure can be implemented to protect the subject.

		The CI must then notify (in the form of a substantial amendment) the MHRA and the REC, in writing, of the measures taken and the reason for the measures within three days of taking the Urgent Safety Measure or as soon as possible for any period during which a disease is pandemic and is a serious risk to human health or potentially serious risk to human health. This notification must include a covering letter detailing the measures taken, the reason for them, the medical assessor contacted and any supporting documentation. The notification must be submitted to the MHRA as per their current submission guidelines on the MHRA website. Should the trial be temporarily halted, or an amendment is required following an event for any reason please see SOP 17a and 17b for guidance.
For externally sponsored (hosted) Studies		
23.	Site Principal investigator	**Use external sponsor's forms and SOPs, report incidents via QMUL and Trust systems.** Report SAEs and SUSARs as per external sponsor's procedures using the external sponsor's forms. Ensure that research team is trained and complies with the study specific pharmacovigilance reporting requirements. If any SAE or SUSAR meets Barts Health NHS Trust or Queen Mary University of London's incident reporting standards, ensure that appropriate procedures are followed. Please see Barts Health NHS trust intranet for the Adverse Incident Policy for details of how to report these events/incidents
24.	Externally Sponsored trials	**There is no need to send the JRMO reports and SAEs for externally sponsored studies, i.e. sponsored by pharmaceutical company or another university or Trust.** The JRMO does not require SAE reports or SUSAR reports, Annual progress reports and Development Safety Update for externally sponsored CTIMPs. These documents need to be processed according to the external sponsor's SOP. The JRMO does not review nor is it obliged to keep copies of these documents.

List of Appendices

Document	Document name
A.	Guidance of RSI

List of Associated documents

Document	Document name
Associated Document 1	Adverse event reporting flowchart.
Associated Document 2	BH/QMUL SAE template form including CIOMS European Serious Adverse Reaction reporting form.
Associated Document 3	Development Safety Update Report template for submission to MHRA
Associated Document 4	DSUR Sample cover letter
Associated Document 5	BH/QMUL Pregnancy reporting and follow up form

Change Control

This section outlines changed from version 11.0 to version 12.0.

Section Changed	Summary and description of change
All	Typos and minor corrections
Sections 19 and 20	Addition of: independent medical advice from Professor of Women's Health and Clinical Epidemiology in case of pregnancy.
Section 12 and 13	Addition of: independent review from Clinical Director for Research and Development

	in case of CI/PI dispute when assessing SAEs.
Section 21	Annual Reports: Addition of APR submission deadlines.

Appendix A Guidance of RSI

The CI must ensure that the protocol defines the reference safety information (RSI) for the trial.

The reference safety information (RSI) must be assessed annually as part of the DSUR submission (see point 17). If there are any changes to the (RSI) during the trial the CI must assess along with the sponsor whether or not the protocol and patient facing documents (patient information sheet and consent forms) need to be formally amended.

Once a decision has been made that an update to the RSI document is required it is important that the change is managed in a timely fashion. The overall process to change the RSI requires several steps, such as a review of the evidence of the proposed change, agreeing the wording, compiling a variation document (where required) awaiting approval by the Competent Authority (where required), notifying relevant parties of approved updates and implementing changes within an appropriate timeframe. It is not possible to define the timeline for the whole process but the CI should ensure that the updates of the SmPCs and IBs are performed without undue delay, as they provide vital information to patients and prescribers that will impact upon patient safety.

The Investigator brochures or SmPC must be reviewed periodically, to ensure that it is up to data and accurately reflects the knowledge currently available about the product. IBs should be reviewed at least annually and revised as necessary. The requirements for reviewing SmPCs is less well defined, although the Directive 2001/83/EC requires that the information should be updated on a ‘regular basis,’ which JRMO has set the standard as being at least annually.

Once approved by the sponsor and Competent Authority (where required), the CI must ensure that the latest version of the RSI, i.e. the SmPC or IB, is distributed to the PI at each site at the commencement of the trial and when updated. The previous version must be superseded in the TMF and a copy of the updated document placed in the file.