Joint Research Management Office Standard Operating Procedure for:			
Non-Compliance and Serious Breach reporting			
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Background:

Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928, contains a requirement for the notification of 'serious breaches' of Good Clinical Practice (GCP) or the study protocol, by the sponsor to the Medicines and Healthcare products Regulatory Agency (MHRA) within 7 days of becoming aware of that breach. NHS Research Ethics Committees (REC) also require serious breaches to be reported to the approving REC within 7 days.

Purpose:

The purpose of this standard operating procedure (SOP) is to describe the management of incidences of non-compliances, potential serious and serious breaches in medical research across Barts Health NHS Trust (Barts Health) and Queen Mary University of London (Queen Mary). This SOP describes recording, corrective and preventative actions (CAPA), root cause analysis (RCA) establishment and escalating these incidences.

Scope:

This SOP is applicable to all staff (including Joint Research Management Office (JRMO) staff) and students involved in medical research taking place at Barts Health and Queen Mary. This SOP applies to all clinical research sponsored or hosted by Barts Health or Queen Mary.

It is the responsibility of all staff involved in a study to identify incidences of non-compliance and report potential serious breaches occurring during the day to day running of a clinical trial to the sponsor. The sponsor is responsible for assessing potential serious breaches to decide whether the event is considered to be a serious breach and for notifying the regulatory authority of these.

Abbreviations:

Barts Health	Barts Health NHS Trust
CAPA	Corrective Action Preventative Action
CI	Chief Investigator
GCP	Good Clinical Practice
IRAS	Integrated Research Application System
JRMO	Joint Research Management Office
NHS	National Health Service
PI	Principal Investigator
QA	Quality Assurance
QMS	Quality Management System
Queen Mary	Queen Mary University of London
SOG	Sponsor Oversight Group
SOP	Standard Operating Procedure

Definitions:

CAPA: A corrective action is the initial response to rectifying the non-compliance. A preventative action is what procedure is put in place to prevent the non-compliance occurring again.

Day 0: Is the date that the sponsor is first informed that a potential serious breach has occurred.

Hosted studies: Studies that are sponsored by organisations external to Barts Health and Queen Mary i.e., NHS Trusts other than Barts Health, universities other than Queen Mary or commercial companies.

Interventional Studies: Research involving a change in treatment, care or other services made for the purpose of the research.

JRMO Non-Compliance meeting group: A JRMO group of senior managers who meet to address all non-compliances that occur in studies sponsored and hosted by Barts Health/Queen Mary.

MHRA-regulated studies: a clinical trial of an investigational medicinal product (CTIMP), advanced therapy investigational medicinal product (ATIMP), or a clinical investigation (e.g., clinical trial of non-CE marked medical device or medical devices used outside of their CE marking).

Non-compliance (in relation to clinical studies): A breach or deviation from clinical study protocols, written procedures, GCP and/or applicable regulatory requirement(s).

Non-Compliance log: The JRMO non-compliance log is a record of all non-compliances reported in medical research across Barts Health/Queen Mary. The log is stored electronically as part of the JRMO quality management system (QMS). It is managed and maintained by the Quality Assurance (QA) Manager.

Non-serious breach (of GCP or the study protocol): a deviation from clinical trial protocols, written procedures and GCP that do not result in harm to Study participants' or significantly affect the reliability of study data.

Research Studies: Any study related to human research where no physical intervention is occurring.

RCA: The retrospective analysis of a non-compliance to assess the underlying cause of the event.

Serious breach (of GCP or the study protocol): a breach which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects of the study or
- The scientific value of the study.

Sponsor oversight group (SOG): A JRMO group of senior managers and the Clinical Research Directors that meet to address significant issues in the conduct of studies sponsored and hosted by Barts Health/Queen Mary.

Relevant SOPs:
SOP 16a Data Protection for research studies

SOP Text:		
	Responsibility	**Activity**
1.	All (JRMO staff, Chief Investigator (CI), Principal Investigator (PI), research team, sponsor, third parties)	**Identify the occurrence of a non-compliance** All non-compliances/breaches must be reported and recorded for the duration of the study. Upon becoming aware of a non-compliance, report it directly to the JRMO GCP and Governance Manager/QA Manager or via email to research.safety@qmul.ac.uk. The email should include the words “Non-Compliance report “in the subject header. See *associated document 1 non-compliance document guidance document* for further details. The JRMO may request completion of a non-compliance notification form to capture further information where necessary (*Associated document 2 Non-Compliance notification form)*
	Potential Serious Breach	
2.	CI/PI/Study team	**Notify the sponsor immediately of any potential serious breaches.** If the study is sponsored by Barts Health or Queen Mary, the JRMO GCP team must be notified of any potential serious breaches, by telephone or emailing research.safety@qmul.ac.uk ensuring the GCP & Governance Managers/QA Manager are copied into the email. As much information as possible should be provided. This initial notification is day 0 and the 7-day period for notification to the MHRA (Where relevant) commences here. The initial notification, if made by telephone, should be followed by written notification of the potential serious breach. The CI/PI (or delegate) should send the notification form to the sponsor representative within 24hrs of becoming aware of the potential serious breach.

		If the incident involves a Barts Health patient or staff member, consider if it meets the requirements of the Barts Health Incident Reporting policy, as necessary. If the incident is related to confidentiality or data protection, please see SOP 16a Data Protection for research studies for further contact and reporting details.
Barts Health and Queen Mary sponsored studies		
3.	JRMO GCP & Governance Manager	**Review the event.** When notified of a potential serious breach, the information should be reviewed in a timely manner to ensure that the event can be reported, if necessary, to the MHRA and/or REC within 7 calendar days Any additional information required should be requested from the study team. The Quality Assurance (QA) manager will log the breach on the non-compliance log, update with all significant information and retain all pertinent correspondence. For further details see *Associated document 1 Non-Compliance guidance document.*
4.	JRMO GCP & Governance Manager/QA Manager	**Assess the event and decide if it is a serious breach.** Once the necessary information has been received, the GCP & Governance Manager/QA Manager must assess the event and decide whether it is a serious breach (please refer to the MHRA/HRA website for further guidance on the notification of serious breaches of GCP or the trial protocol). For studies that are ongoing in the UK, if a serious breach is identified at an investigator site outside the UK that has a significant impact on the integrity of study participants at that non-UK site and is likely to have a significant impact on the integrity of study subjects in the UK, then this will require notification to the MHRA. If the event meets the criteria of a serious breach for a sponsored MHRA regulated study, complete the '*MHRA Notification of Potential Serious Breach of GCP or Trial Protocol' form (see Associated Document 3).* If the event meets the criteria of a serious breach for a sponsored Interventional or Research study, complete the '*Notification of Serious Breach of GCP or Trial Protocol' form for Interventional/Research studies (see Associated Document 4).* In most cases the CI/PI and research team will agree with the assessment on whether a serious breach has occurred. However, if a difference of opinion remains following extensive discussions the event should be escalated to the Research Governance Operations Manager/Senior Operations Manager/SOG members for a decision; and the reasons behind the decision made should be documented and filed appropriately.

5.	JRMO GCP & Governance Manager	**For Sponsored MHRA-regulated studies notify the MHRA about the serious breach within 7 days.** Details about how to submit to the MHRA can be found on the MHRA website. Ensure the notification sent to the MHRA includes the agreed corrective and preventative actions. Also ensure that a copy of the notification is sent to the study team and filed in the JRMO sponsor oversight files. The MHRA will confirm receipt of the serious breach.
6.	CI (Or delegate)	**Notify the REC about the serious breach** For MHRA regulated studies. Notify the REC within 7 days. A copy of the notification sent to the MHRA, and a cover letter should be submitted to the REC. This can be emailed or posted to the REC which approved the study. A copy of these documents should be sent to the JRMO GCP & Governance Manager to review before submitting to the REC. For Interventional/Research studies Notify the REC within 7 days. A cover letter should be submitted to the REC. This can be emailed or posted to the REC which approved the study. A copy of these documents should be sent to the JRMO GCP & Governance Manager to review before submitting to the REC.
7.	JRMO GCP & Governance Manager /CI (Or delegate)	**Provide relevant information and follow up to the MHRA and/or REC.** The GCP & Governance Manager and CI (or delegate) should work together to provide relevant additional information to the MHRA and/or REC and follow up any further actions the MHRA and/or REC request. The GCP & Governance Manager and CI (or delegate) must ensure all required actions are completed and that the breach is then closed. The MHRA will formally email to state no further information is required. The REC will acknowledge in writing and further information or clarification may be requested until the event is closed.
Serious breaches for Barts Health and Queen Mary Hosted studies		
8.	PI (or delegate)	**Inform the JRMO of potential serious breach and forward all relevant paperwork.**
9.	JRMO GCP & Governance Manager / QA Manager	**Review potential serious breach** Review serious breach and record with study documentation. As it is the sponsor's responsibility to assess the breach and ensure resolution, the GCP & Governance Manager will assist only where requested or where necessary.

Non-Compliance reporting for all study types (Non-Serious breach)		
10.	QA Manager or agreed delegate/ Senior GCP and Governance manager	**Initial review of the non-compliance and escalate if required.** Confirm receipt of the non-compliance notification, via email, to the sender of the event. Review and assess the non-compliance and request any follow-up details. Review event and if major or critical or a potential serious breach discuss with the GCP manager. Agree who from the Governance section, where applicable, would be the owner of the event. The owner will ensure the CAPA is completed. Following review and assessment, should the QA Manager have any immediate concerns, the event will be escalated to the Senior GCP and Governance manager or delegate. Following review and assessment, if the Senior GCP and Governance Manager has any immediate concerns, the event will be escalated to the Research Governance Operations Manager.
11.	QA Manager or agreed delegate	**Add event to JRMO non-compliance log.** The QA manager will log the incident on the non-compliance log, categorise as appropriate, update with all significant information and retain all pertinent correspondence. Further details see *associated document 1 guidance document*.
12.	QA Manager / GCP and Governance Managers	**Ensure that each non-compliance is actioned and subsequently closed.** The QA Manager will work with the GCP and Governance Managers (and where applicable the event owner) to ensure all non-compliances are actioned, with sufficient CAPA plan in place and subsequently closed; and that all relevant documentation is filed in the JRMO sponsor oversight file.
Further escalation, review follow up of all events		
13.	QA Manager/Non-Compliance Owner/Study Group	**RCA** RCA process will be implemented where events are reported as a serious breach, non-compliances are classified as critical, where multiple majors occur in one study or where a non-compliance remains unresolved or a direct CAPA plan is difficult to establish. The *RCA proforma (Associated Document 5*) is used to document this procedure. Further details on RCA can be found in *AD1 JRMO Non-Compliance guidance document.*

14.	Non-Compliance group	**Non-Compliance meeting review** The Non-Compliance meeting occurs approximately every 6 weeks and reviews entries on the non-compliance log for that meeting period. The QA Manager prepares papers of all open and closed non-compliances for the group to review. Updates on all open non compliances will be provided by the owner of the non-compliance or group representative. The group will review and discuss all open non-compliance trends, any serious or persistent non-compliance and agree actions to be taken to secure compliance and prevent reoccurrences. At this stage, the group may decide a triggered monitoring or audit visit would be appropriate action. The group will review all closed non-compliances for that meeting period to agree correct actions have been taken. At this stage, the group may decide to re-open a non-compliance where further CAPA details are required.
15.	QA Manager or agreed delegate	**Escalating non-compliances.** The non-compliance meeting group may deem it necessary to escalate a non-compliance based on severity. The event will initially be discussed at the next scheduled QMS meeting. If review and assessment of the non-compliances by the QMS meeting group identifies serious and/or persistent non-compliance on the part of an investigator/institution the Research Governance Operations Manager will escalate the event(s) to the SOG. The SOG where necessary will assess which parties should be notified (e.g., sponsor, medical director) as needed, and any sanctions necessary (e.g., removing site approval/sponsorship, full investigation, temporary halt to a study).
16.	SOG	**SOG review** Members of the SOG will receive papers detailing all open and closed non-compliances for that time period to review as part of the sponsor SOG meeting, which occurs approximately every 3 months. At each meeting, the Research Governance Operations Manager and/or GCP and Governance Manager will present updates on escalated non-compliances. The group will review and discuss non-compliance trends, any serious or persistent non-compliance and agree actions to be taken to secure compliance and prevent reoccurrences.
		Event Closure
17.	QA Manager or agreed delegate	**Non-compliance closure notification** When a non-compliance has sufficiently been action and is closed, the QA Manager will provide the study group with a completed *non-compliance closure notification (AD 6)* by email.

Change control

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

Section changed	Summary and description of changes
All sections	Merger of SOP 31 and SOP 37
All sections	Notification email changed to research.safety@qmul.ac.uk
Definitions	Updated definitions section
Section 1	Completion of the non-compliance notification form will be requested rather than mandatory

List of appendices

There are no appendices associated with this SOP.

List of associated documents

Document ref.	Document name
Associated Document 1	Non-Compliance guidance document
Associated Document 2	Non-Compliance notification template
Associated Document 3	MHRA Notification of Potential Serious Breach of GCP or Trial Protocol' form
Associated Document 4	Notification of Serious Breach of GCP or Trial Protocol' form for Interventional/Research studies
Associated Document 5	Roof Cause Analysis Proforma
Associated Document 6	Non-Compliance notification of closure certificate