JRMO Non-Compliance Guidance Document

Contents

Purpose 2
Definitions 2
Reporting a non-compliance 3
Non-Compliance Log 5
Non-compliance Classification 6
CAPA 9
- CAPA Plan process 9
- CAPA Plan Writing Tips 9
- Common issues with CAPA Plans 9

Root Cause Analysis and Impact Assessment procedures 10
- Organising and conducting 10
- Describe/Outline the event 10
- Collect Data 10
- Review the system 10
- Solution implementation 11
- Monitoring actions 11

Purpose

The purpose of this guidance document is to provide more detailed information on the management of non-compliance in medical research across Barts Health NHS Trust (Barts Health) and Queen Mary University of London (Queen Mary), in support of Joint Research Management Office (JRMO) *Standard Operating Procedure (SOP) 31 Non-Compliance and Serious Breach reporting.*

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.

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-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.

Root Cause Analysis (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.

Reporting a non-compliance

Non-compliances can be identified from several aspects of medical research including, however not exhaustive to:

- Sponsorship deviations
- Procedure deviations
- Good Clinical Practice (GCP) & regulatory deviations
- Audit findings*
- Monitoring Findings*
- Procedure waivers
- DATIX reports
- Internal Procedure reviews
- Training issues

*Audit and Monitoring findings will not be managed by the JRMO non-compliance group unless they are deemed a potential serious breach.

The need for such non-compliances to be managed by the JRMO is assessed on receipt of the event details. It is better to over report than to under report incidences.

If the finding is deemed a potential serious breach, the escalation will be managed by the GCP and Governance and Quality Assurance (QA) Managers.

If the finding is not a serious breach, this will be noted, and the finding will be managed by the auditor in accordance with SOP 22 Audits or monitors in accordance with SOP 28 Monitoring.

Monitoring findings which remain unresolved within specific timeframes by the assigned studies groups may require escalation which will be noted on the non-compliance log.

Where trends in audit and monitor findings are identified, the GCP and Governance and QA Managers will be notified and assessed for management by the JRMO Non-Compliance group.

Where a non-compliance occurs at a study coordinating level, all category of deviations will be logged and managed. Where a non-compliance occurs at a site level, major and critical non-compliances will usually be logged and managed however this will be clarified through the non-compliance meeting group.

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.

The table below details the information captured in the log:

Corrective Action Preventative Action (CAPA)	Proposed and accepted corrective and preventative action plans. Completed CAPAs are noted here.
Category	A detailed list can be found in the Non-Compliance Classification section
Classification	Critical, Major or Other
CTU/Coordinating group	Delegated responsibilities on behalf od the sponsor
Date closed by JRMO	Date of non-compliance closure notification email sent out.
Date Reported to JRMO	Date of email receipt by the JRMO
DATIX	Note if the Non-Compliance was reported via DATIX
DATIX Closed date	DATIX closure date noted by the incident manager
Description	A brief description of the event
Event Type:	A detailed list can be found in the Non-Compliance Classification section
Governance team rep	Where non-compliances relating to amendments, a separate Governance Team representative is assigned if not owned by a member of that team.
IRAS/REDA/ EDGE number	IRAS as preference
Location	Site, department clinical location
Name of CI/PI	CI for sponsored studies, PI for hosted studies
Owned By	Assigned JRMO representative
Ref Number	Each event is given a unique reference number by QA manager
SOG Status	Date the non-compliance was reviewed as part of the SOG meeting or if this was deemed not needed.
Status	Is the non-compliance open or closed
Transferred to indemnity	Once a non-compliance if deemed closed, a final report and pertinent correspondence is filed appropriately.
Trial Short name	Where a short name is available
Type of Study	Sponsored/Regulated/Interventional/Research/Hosted

Non-compliance Classification

Non-compliances are initially classified as “critical”, “major” and “other”.

These classifications are based on the Medicines and Healthcare products Regulatory Agency (MHRA) inspection categories and definitions and are used for all non-compliance events (https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials).

The below are examples and guidance only. They are not an exhaustive list and classifications could vary depending on the judgement of the owner and the Non-compliance group.

A **Critical** finding is classified where evidence exists that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that:

- The safety, well-being or confidentiality of study subjects has been jeopardised.
- Reported findings or integrity of the study are unreliable.
- There are several major non-compliances across areas of responsibility, indicating a systematic QA failure.
- Inappropriate, insufficient or untimely corrective action taken place regarding major non-compliances.
- The incident meets the definition of a reportable serious breach.
- Where provision of the study documentation is not readily available or accessible, or incomplete to such an extent that it cannot form the basis of an inspection, audit or monitoring visit and therefore impedes or obstructs the auditor(s) in verifying compliance.

A **Major** finding is classified where a non-critical finding exists with significant and unjustified departure from applicable legislative requirements has occurred that may not have developed into a critical issue, but may have the potential to do so unless addressed to include:

- Evidence exists that reported findings or integrity of the study may be unreliable.
- Where inappropriate, insufficient or untimely corrective action taken place regarding other non-compliances
- Significant (but not immediate) concerns regarding the safety and wellbeing of study participants
- Evidence of non-compliance with approved SOPs, protocol or other approved study documents.
- Where participant confidentiality or data protection is compromised.
- Where evidence exists that a number of departures from applicable requirements have occurred within a single area of responsibility, indicating a systematic QA failure.
- Evidence of systemic failure to comply with study protocol and procedures, GCP or regulatory obligations or systematic inappropriate delegation of responsibility.
- Lack of appropriate PI study oversight.

A finding will be classified as **Other** where:

- Where evidence exists that a departure from applicable legislative requirements and/or established GCP guidelines and/or procedural requirement and/or good clinical practice has occurred, but it is neither Critical nor Major.
- The event would not be expected to adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.
- Where evidence exists that a departure from applicable requirements has occurred, but it is neither Critical nor Major.
- Non-substantial findings such as administrative errors, misfiling of essential documents, out of date delegation log

Non-Compliances are subsequently categorised by an event type and a category as detailed in the table below:

Event type	Category
Data Protection / IG Deviation	Computer systems
GCP Deviation	Data management (source data and CRF)
Potential Serious Breach	Deviation study procedures
Potential Serious Breach - assessed & not reported	Deviations to GCP/regulations
Protocol Deviation (incl. REC, MHRA, HRA Approval)	Essential approval documents
Serious Breach Reported – MHRA and REC	Essential study documents
Serious Breach Reported – REC alone	IMP and non-IMP
SOP / Local Policy Deviation	Inclusion and exclusion criteria
JRMO SOP Waiver	Informed consent procedures
	Other
	Pharmacovigilance
	Randomisation and cohort allocation/un-blinding
	Study equipment
	Training and staffing
	Vendors / contracts / subcontractor/ finance

Corrective and Preventive Action (CAPA)

The GCP and Governance managers along with the QA Manager and the non-compliance owner will work with the study group to develop a suitable CAPA Plan.

The corrective action plan should include a detailed report of how the non-compliance was initially rectified, by whom and when. The preventative action plan should include a detailed report of how the study team plan to prevent this non-compliance happening again. Preventative action should always be achievable within the study group and where timelines are set, should be realistic.

CAPA Plan process

CAPA Plan Writing Tips

- Be clear and concise.
- Break the non-compliance into individual points and answer each one.
- Provide background details where relevant.
  Actions should be achievable.
- Assign realistic completion dates.

Common issues with CAPA Plans

- Proposed actions only address the immediate problem, rather than a larger systemic issue to address
- Response focuses on justifying or explaining the cause of the non-compliance rather than proposing ways to fix it.
- Response acknowledges the non-compliance but does not propose actions to correct or prevent it.
- Responses are too detailed (think about the big picture).
- Individual points are “missed” (corrective and/or preventative actions are not proposed to address a finding, without any explanation as to why actions have not been suggested).
- Timelines for completing actions are unrealistic – either too short to be completed, or too long to address the issue in a timely manner.

It is strongly recommended that the Non-compliance owner takes time to discuss CAPA for Critical and major non-compliances with the JRMO RG and GCP and Governance managers.

If created by the study or and a research team external to the JRMO or GCP team, the CAPA plan proposed is then submitted and reviewed by the QA manager and ensure the actions fully address the findings.

Root Cause Analysis and Impact Assessment procedures

A systemic Root Cause Analysis (RCA) and Impact Assessment process will be implemented where 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. RCA can be achieved through several steps:

Organising and conducting

Choose the right team – Clinical staff, Researchers, GCP and Governance Managers, QA leads.
Decide on accountability: Who is ultimately responsible and how do we ensure they received updates/reports during the RCA process.

Describe/Outline the event

Establish what happened in the event from all people involved both directly and indirectly. This must be done as soon as possible after the event or incident. Questions to consider are:

- What happened?
- Where did it happen?
- When did it happen?
- Who was involved?
- How did it happen?

Collect Data

Establish what evidence is available relating to the event. This can include equipment, records, location, environmental factors. Establish how long the problem relating to the even have been occurring and the impact this is having on the study.

Review the system

List as many relevant factors relating to the system being followed which led to the non-compliance occurring. Detail the sequence of events, conditions, procedures being followed to try and identify all possible causal factors leading to the event.

Review all processes and systems. Consider what procedures are in place and are they being used. Identify what has failed (Not who) and list the failures to the system, and the potential risk to current procedure. . Decide on which type of failure this falls under:

- Active failures: Unsafe act that are directly linked to the non-compliance
- Latent failures: Less apparent failures that are often hidden until they contribute to the occurrence of a non-compliance or allow non-compliances to go unrecognised.

At this stage an apparent failure should have been identified. The root cause can now be established using the five why’s system. Start by asking why the problem occurred then write it down. If this doesn’t directly answer the source of the problem the ask why again and write

down. Continue to do this until the root cause has been identified and agreed. This may take fewer than five why's or more.

Solution implementation

What can the study group implement to prevent this event occurring again based on Causal factor(s) identified. How will this be implemented and achieved. Identify who would be responsible for this action.

Monitoring actions

Observe the effectiveness of the actions implemented. Re-visit the RCA process if further changes are required.

The RCA and Risk Impact Assessment template 1 can be used to document this procedure.