STANDARD OPERATING PROCEDURE

Serious Breach of Protocol or GCP

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RESEARCH AND INNOVATION

R & I

BACKGROUND

The International Conference of Harmonisation Good Clinical Practice 'is a set of internationally recognised ethical and scientific quality requirements that must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects' (Good Clinical Practice Guide, 2012).

Compliance with this good practice provides assurances that the rights, safety and well-being of research participants are protected, and that the results of the research are of a high quality to ensure they are credible and accurate.

In the UK, the introduction of The Medicines for Human Use (Clinical Trials) regulations 2004 made compliance with the principles of Good Clinical Practice a legal requirement. The Sponsor, or a person legally authorised by the Sponsor of the Clinical Trial, informs the licensing authority in writing within seven days of becoming aware of the serious breach.

PURPOSE

The aim of this SOP is to describe the processes to be followed for identifying, recording and reporting a serious breach of Good Clinical Practice and / or approved trial protocol at Lancashire Teaching Hospitals NHS Foundation Trust.

It is the policy of Lancashire Teaching Hospitals NHS Foundation Trust that the ICH GCP principals are observed in all forms of research.

Identification and Judgement of Serious Breaches

The judgement on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors, for example, the design of the trial, the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, the impact of excluding the data from the analysis etc. It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial.

For the purpose of this Standard Operating Procedure examples of serious breaches of Good Clinical Practice and protocol non-compliance are:

- Breach of GCP leading to hospitalisation, permanent disability or death. Please note, not every Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR) are routinely classified as breaches, but SAEs / SUSARs resulting from a breach of principals of GCP or Protocol deviation may constitute a serious breach.
- Proof of fraud relating to clinical trial records or data where fraud would have a significant impact on integrity of trial subjects or scientific integrity.
- Persistent or systematic non-compliance with GCP or the protocol that has a significant impact of the integrity of trial subjects.
- Failure to control investigational medicinal products such that trial subjects or the public are put at risk or scientific integrity of trial is compromised.
- Failure to report adverse events, SAEs and SUSARs in accordance with legislation.

SCOPE

This SOP applies to all researchers participating in or running research studies being conducted at Lancashire Teaching Hospitals NHS Foundation Trust, including members of the Monitoring and Audit Team.

This also applies to all members of Lancashire Teaching Hospitals NHS Foundation Trust Research & Innovation staff who manage, co-ordinate or advise on clinical research sponsored by Lancashire Teaching Hospitals NHS Foundation Trust.

DEFINITIONS

Protocol: A document that described the objective(s), design, methodology, statistical considerations, and organisation of a trial.

Protocol Non-Compliances: departures from the protocol that have been identified retrospectively. Non-compliances are often technical deviations which do not have a significant impact on the safety or physical or mental integrity of the subjects of the trial or the scientific value of the trial.

Serious Breach: a 'serious breach' is a serious non-compliance with the protocol or with GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial.

Urgent Safety Issues: A protocol deviation / change may be implemented in response to an immediate hazard to a study subject without prior approval. However, the Sponsor will need to be informed within 24 hours.

PROCEDURE

1. WHO?

The Principal Investigator and research team are responsible for the identification and documentation of all protocol non-compliance and serious breaches. They are to inform both Sponsors, in accordance with sponsor guidelines, and the R & I Quality Lead, in order for appropriate corrective and preventative actions to be taken.

Investigator: The investigator is responsible for identifying the serious breach or non-compliance of the trial / study protocol, reporting them to the Sponsor. All serious breaches of GCP or non-compliance of the study / trial protocol must be communicated to the sponsor and documented.

If the Investigator is unsure whether a deviation or violation is a potential serious breach, they should notify the Sponsor as soon as possible and provide as much information as possible.

Study Teams: Study team members are responsible for identifying any serious breaches and reporting to the CI / PI and the Sponsor

Staff involved in Serious Breaches must consult the MHRA web pages on Serious Breaches in conjunction with this SOP to ensure that the most up to date guidance is followed. Good clinical practice for clinical trials - GOV.UK (www.gov.uk)

Information regarding possible serious breaches should be treated as confidential. Details and ensuing investigations will be made available to staff on a need-to-know basis. All individuals interviewed during any investigations will be asked to respect this confidentiality.

Sponsor: The Sponsor is responsible for receiving notification of serious breaches, working with the CI / PI and team to assess the potential serious breach, reporting serious breaches to HRA/REC (and to MHRA if CTIMP), developing CAPA for serious breaches in consultation with the CI, assessing the any proposed CAPA for non-serious breaches and supporting implementation of CAPA.

2. WHEN?

Any serious breaches must be reported to the PI, Sponsor and often the Chief Investigator within 24 hours of them becoming aware of the breach. It is expected that this process be detailed to the research team within the Sponsor documentation provided during the Site Initiation Visit. If the PI/CI or Sponsor is unavailable within the 24hour timeframe, the possible breach must be discussed with the R&I Quality Lead.

3. HOW?

Studies with an external Sponsor (both commercial and non-commercial)

1. The Principal Investigator (PI) or other member of the research team involved in the conduct, management or monitoring of the study identifies that a suspected serious breach of GCP or protocol has occurred. If the breach is identified by a member of the research team, they must inform the Principal Investigator. Information received in written form must be retained. Where communication is verbal, a written record should be generated. This documentation should be stored in the Investigator Site File.

2. The PI reports the suspected breach / non-compliance to the Sponsor and the R & I Quality Lead within 24 hours of becoming aware. If there is a study specific procedure to follow to inform Sponsors of non-compliance and breaches, that should be followed. Following on from the initial report, a full investigation must be completed in conjunction with the study team. Reports of potential serious breaches should provide details of when the breach occurred, the location, who was involved, the outcome and any information given to participants. The possible breach should be recorded on a Study Protocol Deviation Log. If one is not provided by the Study Team, RD-TMP-41_Deviation Log can be used. All reports and accompanying communications must be provided in writing and signed and dated and filed in the Investigator Site File.

3. If the PI deems that the non-compliance would not be classed as a serious breach, the Sponsor should still be informed so that they can make an evaluation of whether it constitutes a serious breach.

4. Where the non-compliance is picked up by the Sponsor, if deemed to be a serious breach or serious non-compliance the Principal Investigator (PI) and / or member of the research team need to inform the R & I Quality lead in writing, including details of the study, PI, and details of the incident.

5. The PI and research team will need to complete a DATIX and CAPA: Corrective and Preventive Actions form (RD-TMP-23_CAPA Form Template Documents | Lancashire Teaching Hospitals Intranet (lthtr.nhs.uk). Once completed, a copy needs to be sent to the R & I Quality Lead. If the Sponsor provides a study specific CAPA this should be used instead of the Trust version.

6. The R & I Quality Lead will inform the R&I Safety and Quality Group and request an immediate review, to decide upon the course of action required, such as:
   - Whether a triggered audit should be called
   - Call a temporary halt to further recruitment.
   - Further escalation to the Head of R&I, R&I Committee or another Trust Committee.

7. The PI keeps the Centre for Health Research and Innovation informed, in writing, of all communications with outcomes of reviews conducted by Sponsor, HRA and REC, including where the Sponsor decides to temporarily halt recruitment or suspend the study.

8. The Quality Lead tracks the serious breach/CAPA through the OneDrive CAPA programme, until conclusion, and ensures that outcomes are escalated appropriately to the relevant personnel. The CAPA will be reviewed accordingly post-breach by the Quality Lead, automated emails are sent to the Quality Lead through OneDrive when reviews are due. All members of the R&I Risk Working Group have access to the OneDrive CAPA system.

Where the sponsor categorises the non-compliance as non-serious

1. The PI or research team member undertakes the action required by the Sponsor, (e.g. patient withdrawn or continues). The Sponsor may also request a study specific CAPA be completed, this should be stored in the Investigator Site File. A copy of the CAPA should be provided to the R&I Quality Lead. Guidance should be sought from Sponsors regarding the timeframe as this may vary.

2. If previously reported to the R&I Quality Lead that the non-compliance was a serious breach, then the PI or delegated person informs the R&I Quality Lead in writing of the Sponsor decision.

3. Even for non-serious breaches it may be worthwhile completing a CAPA. Ensure you discuss with your team lead / manager, the R&I Clinical Lead or Quality Lead to determine if a CAPA is required.

Studies Sponsored by Lancashire Teaching Hospitals NHS Foundation Trust

1. The Chief Investigator (CI), or other member of the research team identifies that a breach of GCP or protocol has occurred. If the breach is identified by a member of research team, they inform the Chief Investigator in writing, within 24 hours.

2. The CI reports the non-compliance to the Sponsor representative and R&I Quality Lead in writing, within 24 hours of becoming aware. Reports of serious breaches should provide details of when the breach occurred, the location, who was involved, the outcome and any information given to participants.

3. The CI and Sponsor make an evaluation of whether the non-compliance constitutes a serious breach. This decision should be documented in writing and filed in the Investigator Site File.

4. As per the Medicines for Human Use Clinical Trials Regulations, the Sponsor / CI is responsible for informing the relevant regulatory authorities including the Health Research Authority (HRA), Research Ethics Committee (REC) and Medicines and Healthcare products Regulatory Agency. The MHRA Notification of Serious Breaches form, GCP Serious Breaches update - MHRA Inspectorate (blog.gov.uk) should be used and sent to **GCP.SeriousBreaches@mhra.gsi.gov.uk**. It is a requirement that all serious breaches on CTIMP studies are reported to the MHRA within seven days of the Sponsor becoming aware. The HRA and REC that granted original approval must also be notified in this tie for both CTIMP and non-CTIMP studies.

5. If there is not clear and unequivocal evidence of a serious breach, then further investigation and assessment by the CI and Sponsor representative may be required prior to notification of the MHRA. In this case the MHRA GCP inspectorate must be contacted to seek advice.

6. The CI and research team will need to complete a CAPA: Corrective and Preventive Actions form (RD-TMP-23_CAPA Form, Template Documents | Lancashire Teaching Hospitals Intranet (lthtr.nhs.uk). Once completed this needs to be sent to the R & I Quality Lead.

7. The CI, along with the Sponsor and R & I Quality Lead will liaise to decide upon the initial course of action required, followed by feedback to the R&I Safety and Quality Group. Actions may include:
   - Whether a triggered audit should be called
   - Call a temporary halt to further recruitment.
   - Escalation to R&I Manager and Director of Research and Innovation, R&I Committee or another Trust Committee as required.

8. The regulatory authorities including MHRA may provide advice on any urgent measures that will need to be implemented immediately. The Sponsor will be responsible for gaining this advice.

9. The Quality Lead tracks the serious breach until conclusion and ensures that outcomes are escalated appropriately to the relevant personnel. The CAPA will be reviewed two months post breach by the Quality Lead. The research teams should ensure that they monitor the progress of the CAPA and report to the Quality Lead.

10. All correspondence and documentation relating to the breach must be retained and copies filed in the Trial Master File and Investigator Site File.

SUPPORTING DOCUMENTS:

Guidance for the notification of serious breaches of GCP or the trial protocol
MHRA Notification of Serious Breaches form GCP Serious Breaches update - MHRA Inspectorate (blog.gov.uk)
RD-TMP-23_CAPA Form
RD-TMP-41_deviation log

CONSULTATION WITH STAFF AND PATIENTS

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R&I Safety and Quality Group	Approval
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Signature		**Date**	21-03-2024

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