Notification of Serious Breaches of Good Clinical Practice or the Trial Protocol

NJRO-REG-SOP-013

Contents

1. Background/Introduction

It is a requirement under the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended by Statutory Instrument (SI) 2006/1928, that all serious breaches of Good Clinical Practice (GCP) and/or the trial protocol must be reported to the Medicines and Healthcare products Regulatory Agency (MHRA).

Regulation 29A of Statutory Instrument 2006/1928 states:

"(1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

a) the conditions and principles of GCP in connection with the trial; or

b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, **within seven days** of becoming aware of that breach.

(2) For the purposes of this regulation, a "serious breach" is a breach 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".

This is also reflected within the Standard Operating Procedures for Research Ethics Committees (REC) (September 2022), which states: 'The sponsor should notify the REC and relevant regulatory bodies of a serious breach in any study within 7 days of the matter coming to their attention.'

2. Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the process for the notification of suspected serious breaches of GCP and/or the study protocol for research within the Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH).

3. Scope of Document

This SOP applies to all staff involved in research sponsored and hosted by NuTH.

This SOP is also applicable to members within the Newcastle Joint Research Office (NJRO) who act as sponsor representatives on NuTH sponsored studies and to those who oversee hosted research.

This SOP also applies to all trial management staff working on NuTH sponsored research.

4. Definitions

ATIMP: Advanced Therapy Investigational Medicinal Product

CAPA: Corrective And Preventative Action

CI: Chief Investigator

CRO: Contract Research Organisation

CTIMP: Clinical Trial of an Investigational Medicinal Product

CTU: Clinical Trials unit

GCP: Good Clinical Practice

MHRA: Medicines and Healthcare products Regulatory Agency

NJRO: Newcastle Joint Research Office

NuTH: Newcastle upon Tyne Hospitals NHS Foundation Trust

PI: Principal Investigator

RCT: Regulatory Compliance Team

REC: Research Ethics Committee

SI: Statutory Instrument

USM: Urgent Safety Measure

5. Roles & Responsibilities

As per SI 2004/1031, Regulations 28 and 29, **no person** shall conduct a clinical trial otherwise than in accordance with:

- the conditions and principles of GCP;
- the approved protocol (unless an USM is required – see NJRO-GEN-SOP-002);
- the request for authorisation to conduct the trial;
- the application for an ethics committee opinion in relation to that trial;
- any particulars or documents, other than the protocol, accompanying that request or application;

- any conditions imposed by the licensing authority.

It is the responsibility of the Chief Investigator (CI) and Principal Investigator (PI) to ensure that the clinical trial/study is conducted in accordance with GCP and the protocol. This task may be delegated to a suitably qualified or experienced member of the research team but the CI and PI will retain overall responsibility. Where non-compliances occur, the PI (or delegate) is responsible for reporting these to the sponsor, Contract Research Organisation (CRO), Clinical Trials Unit (CTU) or equivalent as described within the study protocol (or alternative documentation). The PI (or delegate) is also responsible for reporting non-compliances to the NJRO as detailed in NJRO-GEN-SOP-002 and for keeping local records of any non-compliances within the Investigator Site File (ISF).

It is the responsibility of the trial sponsor to report all serious breaches of GCP and/or the trial protocol as per the regulatory timeframes to the applicable Research Ethics Committee (REC) and Competent Authority (e.g. MHRA in the UK) where appropriate.

The Regulatory Compliance Team (RCT) are responsible for the review, classification, investigation and expedited reporting of potential serious breaches for all high risk, NuTH sponsored research (unless otherwise stated within a Delegation of Sponsor Duties Agreement or equivalent). This includes NuTH sponsored CTIMPs, ATIMPs, Clinical Investigations of medical devices, high risk surgical trials and applicable international trials.

It is the responsibility of all trial management staff involved in the management of clinical trials sponsored by NuTH to report observations of suspected serious breaches of the protocol and/or GCP to the RCT. This will be documented within a Delegation of Duties Agreement held within the Sponsor Oversight File (SOF).

The Governance Team are responsible for the review, classification, investigation and expedited reporting of potential serious breaches for all low-medium risk NuTH sponsored research (unless otherwise stated within a Delegation of Sponsor Duties Agreement or equivalent document/correspondence).

It is the NJRO's responsibility to oversee the conduct of all NuTH sponsored studies and to ensure compliance with the approved protocol, GCP and applicable regulations.

It is also the responsibility of the sponsor to take appropriate corrective and preventative actions (CAPA) in response to a serious breach, where appropriate.

Site teams, CTUs/trial management staff and the sponsor all have a responsibility to implement any proposed CAPAs as appropriate, and ensure serious breaches are fully documented.

When a clinical trial is hosted but not sponsored by NuTH, notification of an actual or potential serious breach should be directed to the appropriate sponsor contact within the specified timescales. This should be done by the delegated member of the NuTH research delivery team conducting the study, who should also inform the NJRO Governance team of the potential breach as soon as possible via nuth.genericqueries@nhs.net. All correspondence must be saved within the Investigator Site File (ISF). The NJRO Governance team will subsequently engage in further discussions with sponsor (as required) and perform any associated assessment and investigation (as required).

NuTH delivery teams in collaboration with the appropriate NJRO team are responsible for working with sponsors, CROs/CTUs and regulators (where applicable) to provide and input into suitable CAPAs and to ensure these are actioned where necessary.

6. Procedures

The procedure for the notification of serious breaches of GCP and/or the trial protocol consists of the following stages:

Stages of the Notification of a Serious Breach
1) Identification of a potential serious breach & notification to the sponsor and NJRO
2) Assessment of the potential serious breach
3) Notification to the applicable Research Ethics Committees (REC) and Competent Authorities (e.g. MHRA in the UK)
4) Follow up after reporting (including the provision of additional information and the planning and implementation of CAPAs)

Please see further details regarding each stage below.

6.1 Identification and Notification of a Potential Serious Breach to the Sponsor and NJRO

It is the responsibility of the Chief Investigator (CI) and Principal Investigator (PI) to ensure that a study is run in accordance with GCP and the protocol. This task may be delegated to a suitably qualified or experienced member of the research team but the CI and PI will retain overall responsibility.

Where non-compliances occur, the PI (or delegate) is responsible for reporting these to the sponsor, Contract Research Organisation (CRO), Clinical Trials Unit (CTU) or equivalent as described within the study protocol. The PI (or delegate) is also responsible for reporting non-compliances to the NJRO as described in NJRO-GEN-SOP-002.

The PI (or delegate) is responsible for reporting any potential serious breaches as follows:

- **NuTH sponsored high risk clinical trials**: For NuTH sponsored high risk trials, all suspected serious breaches must be notified to the relevant CTU/trial management contact (as per protocol) or directly to sponsor, immediately (within 24 hours). If notification is made to the CTU, the trial manager (or equivalent) must notify sponsor immediately (within 24 hours). The initial contact with sponsor may be made in person, via telephone (by contacting the RCT and stating that a suspected Serious Breach has occurred) or via email to tnu-tr.safetyreporting@nhs.net (please enter SERIOUS BREACH in the subject line).

- **NuTH sponsored low-medium risk studies**: For low to medium risk NuTH sponsored studies, all suspected serious breaches must be notified to the NJRO Governance team immediately (within 24 hours). The initial contact with the Governance team may be made in person, via telephone (by contacting the Governance team and stating that a suspected serious breach has occurred) or via email to nuth.nuthsponsorship@nhs.net (please enter SERIOUS BREACH in the subject line).

- **Hosted studies**: All suspected serious breaches identified within hosted studies at NuTH must be notified to the sponsor representative as per the process set out within the protocol or alternative study documentation. Details should also be forwarded to the NJRO Governance team as soon as possible via: nuth.genericqueries@nhs.net (please enter HOSTED SERIOUS BREACH in the subject line).

When reporting a suspected serious breach to the NJRO, the following information should be provided, if available, from the person reporting the suspected breach:

  - Name of CI/PI
  - R&D reference number
  - Title of the study
  - An explanation of how the breach was identified
  - Details of the breach
  - Date and time of the breach
  - Number of participants affected, with their study identification number(s)
  - Details of any CAPA performed so far
  - Assessment of the impact of the breach on study participant safety or the scientific integrity of the trial.

Upon receipt of a suspected serious breach to the NJRO, the RCT or Governance Team (as appropriate) should initially notify their appropriate manager of the suspected serious breach:

- **NuTH sponsored high risk trials**: RCT should notify the Regulatory Compliance Manager (RCM) and Deputy Regulatory Compliance Manager.
- **NuTH sponsored low-medium risk studies**: Governance team should notify the RCM and Research Governance Manager (RGM).
- **Hosted Studies**: Governance team should notify the RCM and RGM.

A manager within the relevant NJRO team (or an appropriate delegate) will use this information to start completion of the R&D Suspected Serious Breach Form.

In addition to site teams identifying potential serious breaches when conducting the trial, these may also be identified by the NJRO Quality Assurance Team, sponsor, CROs, and CTU/trial management staff during monitoring and audits.

The NJRO QA team may audit the trial as part of the NJRO annual audit cycle. Any actual or suspected breaches identified through audit must be reported to the RCT or Governance team as detailed above, along with the appropriate management staff (as set out above) immediately (within 24 hours). If the appropriate managers are unavailable, notification should be made to the Clinical Director of R&D and Head of the NJRO. If a potential serious breach is identified during an audit for a hosted study, this must also be notified to the study sponsor.

Monitors may also identify suspected serious breaches when performing monitoring activities or during contact with sites. For NuTH sponsored clinical trials, trial management staff must report these to the appropriate sponsor team using the contacts and timelines set out above. When site teams become aware of a suspected serious breach identified during monitoring for a hosted study, these should be notified to the Governance team as soon as possible.

Deviations from clinical trial protocols and/or GCP occur commonly in clinical trials. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. These cases should be documented appropriately in order for any necessary corrective and preventative actions to be taken. In addition, these deviations should be included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data. However, not every deviation from the protocol needs to be reported to the MHRA and/or REC as a serious breach.

Examples of what may and may not considered serious breaches by the MHRA are included in Appendix 8.1.

6.2 Sponsor Assessment of a suspected Serious Breach

The judgement regarding whether a potential serious breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors such as trial design; the type and extent of the research data affected by the breach and its overall contribution to key outcome measures. It is the responsibility of the sponsor to assess the impact of the breach on the scientific value of the trial.

This assessment should be documented, as the appropriateness of the decisions taken by the sponsor may be examined during audit and inspection. If the sponsor is unclear about the potential for a breach to have significant impact on the scientific value of the trial, the sponsor should contact the MHRA and/or REC (as appropriate) to discuss the issue further.

Upon receipt of information indicating a suspected serious breach, the sponsor representative may discuss the event with the CI/PI to determine if it constitutes a reportable, serious breach as per MHRA/REC guidance. If necessary, the MHRA or REC should be contacted to discuss the event and obtain further advice. All relevant correspondence and documentation regarding the event should be retained by the NJRO, whether or not the event is ultimately deemed a serious breach.

On behalf of the sponsor the relevant NJRO team (in conjunction with the appropriate manager) will make an initial assessment of the impact on patient safety and/or scientific integrity of the trial, within two (2) working days of becoming aware of the event. This will be documented on the Suspected Serious Breach Form and the decision will also be reported back to the CI.

Where a decision cannot be reached by the NJRO team (or where further input is required, e.g. from a clinical perspective), the NJRO may also consult the Clinical Director of R&D; the Associate Medical Director – Research; the Head of the NJRO and the NJRO Quality Assurance team where appropriate. The relevant NJRO manager (or delegate) will discuss the event with applicable members from the senior management team, further assess the impact on patient safety and/or scientific integrity of the trial and make a decision on whether or not the event constitutes a serious breach.

Any discussion, including the decision, will be documented on the Suspected Serious Breach form. This will be circulated to those consulted via email, signed by all relevant parties and held in the Sponsor Oversight File (SOF), along with all associated email correspondence.

The CI/PI will also be informed of the Sponsor decision via email. If the event is determined to be a serious breach, the appropriate NJRO manager (or delegate) will also inform relevant staff within the Research directorate via email as appropriate.

It is also the responsibility of the sponsor to take appropriate corrective and preventative actions in response to the serious breach, and to document these actions appropriately via the Suspected Serious Breach Form.

In addition, the event must be assessed to determine whether or not it constitutes a serious incident (SI). This is defined as an event or incident that resulted in unexpected or avoidable death, or serious harm, to one or more patients, staff, visitors or members of the public. If the event has been classed as (or is suspected to be) a SI, the appropriate NJRO manager (or delegate) will inform the Director of Quality and Effectiveness, via the Clinical Governance and Risk Department (CGARD), as soon as possible by telephone. (Please refer to NuTH "Serious Incidents (SIs) Reporting and Management Policy" for further information including categories of SIs.)

6.3 Notifying the MHRA and/or REC

For all CTIMPs and Clinical Investigations of Medical Devices which have received a Clinical Trial Authorisation by the MHRA or a Letter of No Objection, if the event is determined to be a reportable serious breach the appropriate NJRO sponsor team will use the available information to complete the MHRA's "Notification of Serious Breach of Good Clinical Practice or Trial Protocol" form (available via the MHRA website). The form must be emailed to GCP.SeriousBreaches@mhra.gov.uk within **seven days** of Sponsor's first awareness of the event.

A copy of the form must also be submitted to the appropriate Research Ethics Committee (REC) within **seven days** of first awareness of the event by a sponsor representative. A copy of the form must be filed in the Trial Master File (TMF) and Sponsor Oversight File (SOF).

For all other research that does not require MHRA authorisation, the Serious Breach must be notified to the appropriate REC within **seven days** of first awareness of the event by a sponsor representative. Again, a copy of the notification must be filed in the TMF and SOF.

The sponsor representative does not have to wait until they have all the information when reporting an initial serious breach, follow-up reports are acceptable. If the investigation or corrective and preventative actions are on-going at the time of reporting the serious breach, it is acceptable to indicate plans with projected timelines for completion. In such case, it should indicated in the initial report when these are

expected to be completed and what follow-up reports will be provided to the MHRA and/or REC and when.

Follow-up reports should be made in writing (the MHRA serious breaches form can be used for this where applicable) and should:

- Be clearly identified as a follow-up report.
- Identify the unique GCP identification/code allocated when the initial report was acknowledged (if this information is known) - (for breaches reportable to the MHRA)
- Follow-up reports should include all previously submitted information with new information added in a clear and transparent way. Each report form should be a complete record up to that point and therefore only the latest form is needed for review.
- Be forwarded to the inspector dealing with your initial notification directly or via the mailbox (for breaches reportable to the MHRA)

If the serious breach has resulted in a temporary halt to the study, a substantial amendment must be submitted to the MHRA Clinical Trials Unit and/or the appropriate REC within 15 days of the halt of the trial (to be completed by the CI (or delegate) or the relevant Clinical Trials Unit (CTU)/trial management staff). To restart a trial that has been temporarily halted, the sponsor should make the request via a substantial amendment providing evidence that it is safe to restart the trial. If the sponsor decides not to recommence a temporarily halted trial, the MHRA and/or REC must be notified in writing within 15 days of the decision, using the end of trial declaration form and including a brief explanation of the reasons for ending the trial prematurely.

If further information is requested by the MHRA or the relevant REC, the appropriate sponsor representative will ensure that a response is submitted in a timely manner.

Upon receipt of the Serious Breach Form, the MHRA and/or REC will review and assess the notification, and a variety of actions may be taken, depending on the nature of the breach and its potential impact. Once any/all required actions have been satisfactorily completed, the inspector will close the referral.

6.4 Following MHRA and/or REC Notification

The serious breach must also be reported via the Trust's DATIX system by a trained sponsor representative if the event occurred at NuTH. (See also NuTH "Management and Reporting of Accidents and Incidents Policy"). If the serious breach occurred at another site, this should be reported by the local site team as per local policy.

After the initial notification to the MHRA and/or REC, the designated sponsor representative will continue to review the serious breach in full to identify the extent of the breach and propose any further corrective and preventative actions. These will be documented appropriately (via the Suspected Serious Breach Form or equivalent) and circulated to the CI and relevant senior management team as appropriate. Depending upon the initial assessment of the breach, a full audit of the trial may be conducted via the NJRO QA team, including a review of the general trial management systems. Any new information will be forwarded to the MHRA and/or REC as appropriate.

The appropriate NJRO manager (or delegate) will work with the study team to devise the appropriate CAPAs to address the breach. The resulting CAPA plan will be submitted to the MHRA and/or REC as part of the investigation report. Monitoring of this plan will be undertaken by the sponsor and by the MHRA (where appropriate), should the trial be chosen for inspection by the Competent Authority. The sponsor representative may also add the serious breach/CAPA to the appropriate senior management meeting for discussion.

The sponsor is responsible for ensuring the follow up and completion of any CAPA items proposed.

7. References

Standard Operating Procedures for Research Ethics Committees. V7.6. September 2022. Available at < https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-committee-standard-operating-procedures/>

Statutory Instrument 2004/1031: The Medicines for Human Use (Clinical Trials) Regulations 2004

Statutory Instrument 2006/1928: The Medicine for Human Use (Clinical Trials) Regulations 2006

MHRA Good Clinical Practice for Clinical Trials: Report a Serious Breach - https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials#report-a-serious-breach

Health Research Authority: Risk in Research: Serious Breach Notifications and Safety Reporting - https://www.hra.nhs.uk/about-us/consultations/closed-consultations/risk-research-serious-breach-notifications-and-safety-reporting-consultation/

NuTH – Serious Incidents (SIs) Reporting and Management Policy

NuTH – Management and Reporting of Accidents and Incidents Policy

8. Appendices

Appendix 1

Examples of Serious Breaches Notified to the MHRA

Breach	Is this a Serious Breach?
One subject was due to receive IMP on day 1 and day 8, but instead received IMP on days 1 to 8 (therefore 6 additional doses). Subject experienced a serious adverse event as a result	**Yes -** there was impact on the safety or physical or mental integrity of trial subjects and on the scientific value of the trial
A subject took IMP that expired two days ago. The subject did not experience any adverse events and this issue was not likely to affect data credibility of trial	**No -** there was no impact on the safety of the subject or scientific value of the trial and this was a single episode.
Patient Information Sheet and Informed Consent Form updated and not relayed to participants at one trial site until approximately 2-3 months after approval	**Yes** – if there was a significant impact on participant safety due to key safety information not being relayed to the subjects in a timely manner **No** – if this was not a persistent problem and there was no harm to the trial participants from the delay
Visit date deviation	**No** – if this did not result in the participant being put at risk, this would likely classify as a minor protocol deviation which does not meet criteria for reporting.
Investigator failed to report one SAE as defined in the protocol	**No** – if it did not result in this or other participants being put at risk and if it was not a persistent problem
Investigator failed to reduce or stop trial IMP, in response to laboratory parameters, as required by the protocol. This occurred with several participants over a one-year period, despite identification by the monitor on first two	**Yes** – identified risk to participant safety and was a persistent issue.

occasions. Patients were put at increased risk of thrombosis.	
IMP temperature excursions reported	**Yes** – if event was unmanaged and subjects dosed with unstable IMP, resulted in actual or potential harm to participants **No** – if the excursions were managed appropriately (e.g., moving IMP to an alternate location/quarantining as necessary) and an assessment from the Qualified Person obtained that there was no impact on stability data for the IMP, therefore no impact on participant safety or data integrity
Early destruction of investigator site files (one study had completed the year before and one was still ongoing)	**Yes** – affects scientific integrity of the trial