Protocol Deviations, Violations, Waivers and Urgent Safety Measures in Studies Sponsored and Hosted by NuTH

NJRO-GEN-SOP-002

Contents

1. Background/Introduction

Adherence to the protocol is a fundamental part of the conduct of a research study. All trials must be conducted in accordance with the protocol agreed by the sponsor and approved by the Research Ethics Committee (REC), Health Research Authority (HRA) and if applicable, the Competent Authority (e.g. the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK) (ICH GCP E6(R2)).

For Clinical Trials of Investigational Medicinal Products (CTIMPs), it is a legal requirement to adhere to the protocol and the principles of Good Clinical Practice (GCP) as defined in regulations 28 and 29 of the UK Statutory Instrument (SI) 2004/1031. For all non-CTIMPs, the UK Policy Framework for Health and Social Care Research (2017) requires all research to be run in accordance with all relevant legislation including the principles of GCP.

As such, Investigators and the wider study team must conduct their trials in accordance with the approved protocol unless an urgent safety measure (USM) is required to eliminate an immediate hazard(s) to study participants (see section 6.9 of this Standard Operating Procedure (SOP) for further details).

2. Purpose

The purpose of this SOP is to describe the procedures at The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) surrounding protocol deviations, violations, waivers and USMs.

3. Scope of Document

This SOP should be followed by all NuTH staff involved in studies sponsored and hosted by NuTH to ensure that all departures from the protocol and/or GCP are recorded and reported in accordance with sponsor procedures and all regulatory requirements. For NuTH sponsored multicentre studies, it is also expected that all service providers (e.g. investigator sites) comply with this SOP.

4. Definitions

The following definitions have been adapted from the 'ICH GCP Integrated Addendum E6(R2) – Section 1' and the MHRA's Good Clinical Practice Guide.

Protocol: A document describing the objectives, design, methodology, statistical considerations and organisation of a trial. The protocol also provides the background and rationale for the trial.

Protocol Amendment: A written description of change(s) to or formal clarification of a protocol.

Protocol waiver: Prospective deviations or waivers to the protocol that are knowingly undertaken. In CTIMPs, protocol waivers are a breach of regulation 29 of SI 2004/1031 and are therefore not acceptable. In non-CTIMPs, waivers go against best practice and will therefore not be accepted.

Protocol Deviation: A change or departure from the protocol and/or GCP that does not result in harm to the study participants or significantly affect the integrity of the reported results.

Protocol Violation: Consistent variation in practice from the defined protocol. A violation is a significant occurrence or event which may affect study participant's rights, wellbeing and/or safety, or the integrity of the research.

Serious Breach: A breach (violation or deviation) of the protocol and/or GCP that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the study participants; and/or
- the scientific value of the study.

Urgent Safety Measure (USM): An urgent action, which deviates from the protocol, taken to protect a research participant from any immediate hazard to their health and safety arising from their involvement within a research project. An USM does not have prior approval from REC, HRA, MHRA or the sponsor.

Corrective and Preventative Actions (CAPA): Corrective and preventative actions taken to eliminate causes of non-compliance and to prevent similar situations from reoccurring again.

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 section 6.9);

- 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.

The PI and study team on site are responsible for identifying deviations and violations as they occur.

For high risk NuTH sponsored clinical trials (e.g. CTIMPs, Advanced Therapy Investigational Medicinal Products (ATIMPs), Device trials etc.), responsibility for reporting deviations/violations to sponsor, completing deviation/violation reports and maintaining the central deviation/violation log is often delegated to a Clinical Trials Unit (CTU) via the sponsor Delegation of Duties Agreement, a copy of which should be maintained in the Trial Master File (TMF) and Sponsor Oversight File (SOF). However, site teams have a responsibility to report all non-compliances to the CTU (or sponsor) as defined in the protocol, and for keeping local records of any deviations/violations that occur within the Investigator Site File (ISF). Site teams, CTU and sponsor all have a responsibility to implement any CAPAs as appropriate.

For NuTH sponsored low-medium risk studies, responsibility for reporting deviations/violations, completing deviation/violation reports, maintaining the deviation/violation log and implementing appropriate CAPAs lies with the Principal Investigator (PI) at each investigator site. However, this may be delegated to an appropriate member of the research team.

It is the responsibility of all trial management staff involved in the management of clinical trials sponsored by NuTH to report observations of suspected deviations, violations, and serious breaches of the protocol and/or GCP to the sponsor.

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 prevailing UK regulations.

For high risk, NuTH sponsored research, the Regulatory Compliance Team (RCT) are responsible for reviewing protocol deviations, violations and serious breaches on behalf of sponsor, and for ensuring appropriate CAPAs are put in place. The RCT is also responsible for reporting serious breaches to the REC and Competent Authority (MHRA in the UK) unless stated otherwise within the Delegation of Sponsor Duties Agreement.

For all low-medium risk NuTH sponsored studies, the NJRO Governance Team maintain responsibility for the assessment of protocol deviations, violations and serious breaches

on behalf of sponsor, and for ensuring appropriate CAPAs are implemented. The Governance Team are also responsible for reporting Serious Breaches to the REC unless otherwise stated within a Delegation of Sponsor Duties Agreement, Protocol or equivalent document.

For all hosted NuTH studies, the delivery teams are responsible for notifying the sponsor of any deviations, violations and serious breaches as they occur. All associated correspondence should also be saved within the ISF.

For all hosted NuTH studies the delivery teams have a responsibility to inform the NJRO Governance team of all serious breaches that occur at site via the trust inbox: nuth.genericqueries@nhs.net. The Governance team will subsequently engage in further discussions with sponsor (as required) and perform any associated assessment and investigation (as required).

Where applicable the appropriate NJRO team has a responsibility to inform UK regulators. In most cases, as appropriate, this will be completed in collaboration with the trial sponsor and Clinical Research Organisation (CRO) or equivalent.

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

6. Procedures

6.1 Protocol Deviations

An unintended (non-serious) departure from the approved protocol and/or GCP that does not result in harm to the participants or significantly affect the scientific value of the reported results would be considered a 'Protocol Deviation'.

Examples of protocol deviations may include a visit conducted outside of the study visit window, and missed or incomplete study procedures which are deemed **not to significantly affect** the scientific value of the reported results or patient safety.

Protocol deviations are usually identified retrospectively via the monitoring and data validation of Case Report Forms (CRFs), e.g. time/visit windows outside those defined in the protocol. However, it is important to note that the CRF will not identify all non-compliances (e.g. such as incorrect sample handling/processing etc.) which can equally impact upon trial results. Therefore it is important that robust procedures are in place to ensure all protocol and GCP non-compliances are captured.

6.2 Protocol Violations

Protocol violations occur when there is a consistent variation in practice from the defined protocol and/or GCP. A violation is a significant occurrence or event that has the potential to impact the accuracy and/or reliability of the study data or affect a participant's rights, safety or wellbeing.

Examples of protocol violations may include the enrolment of a patient that does not meet the inclusion/exclusion criteria; failure to obtain informed consent and/or IMP dispensing, labelling or dosing errors. However, a violation may also be deemed a serious breach if it is likely to affect to a significant degree the safety or physical or mental integrity of the study participants; and/or the scientific value of the study.

A protocol deviation may also become a violation if it occurs on multiple occasions and/or has a significant impact upon multiple participants.

6.3 Identifying Protocol Deviations & Violations

At each participating site, the PI and local study team are responsible for identifying protocol/GCP deviations and violations as they occur.

Deviations/violations of the protocol and/or GCP should also be identified by trial management staff when performing monitoring activities and by sponsor when performing oversight related duties, such as reviewing safety data (e.g. Serious Adverse Event reports), monitoring reports, and when conducting audits etc.

6.4 Recording and Reporting Deviations & Violations to Sponsor

High Risk, NuTH Sponsored Studies:

All deviations and violations which occur throughout a study should be documented within the TMF, SOF and the Investigator Site File (ISF) of the relevant site.

Protocol deviations should be recorded using a deviation log (see associated document NJRO-GEN-T-003, Appendix 1). Where trial management is delegated to a third party, alternative deviation log templates may be used with agreement of sponsor.

Where appropriate, the PI should review the deviation log to confirm that they have been informed of the deviations and that they have provided input in to any applicable CAPA. This review should be documented and filed within the ISF.

For high risk studies, the trial management team are usually responsible for ensuring that deviation logs have been sent by the sites at pre-defined, study specific intervals (as agreed with sponsor during study set up). They then review the deviation logs for completeness and assess whether the proposed CAPA is appropriate. The delegation of these sponsor related tasks will be defined via the Delegation of Duties Agreement, a copy of which should be stored within the TMF and SOF.

For high risk NuTH sponsored trials, the deviation logs should also be submitted to the RCT via the Safety Reporting Inbox: tnu-tr.safetyreporting@nhs.net.

If a deviation is found to have the potential to impact the accuracy and/or reliability of the study data or affect a participant's rights, safety or wellbeing, then this should be reported to the RCT using a Violation Form (see associated document NJRO-GEN-T-004, Appendix 2). Where management is delegated to a third party, alternative violation form templates may be used with agreement of sponsor.

The Violation Form should be completed and submitted to the safety reporting inbox (tnu-tr.safetyreporting@nhs.net) as soon as possible, but within 3 working days of becoming aware of the Violation. This is to ensure that the RCT can perform a timely and thorough review of the event, determine whether the incident classifies as a Serious Breach, and perform a review of all associated CAPAs (see section 6.5 for further details).

Please note that if a suspected serious breach is identified by the site study team or trial management team, these must be recorded on a Violation Form (or equivalent sponsor approved document) and submitted to sponsor within 24 hours of becoming aware of the potential breach via the safety reporting inbox (tnu-tr.safetyreporting@nhs.net). All associated correspondence should be retained in the TMF and SOF.

The documents used for reporting deviations/violations to NuTH as sponsor can vary on a trial by trial basis depending upon the nature of the trial (e.g. outcome of the risk assessment) and the trial management set up (e.g. CTU involvement). Nonetheless, the RCT on behalf of sponsor must review and approve all safety reporting methods (including adverse event and deviation/violation reporting) used within high risk studies before they are implemented.

Low-medium risk, NuTH sponsored studies:

For low-medium risk NuTH sponsored studies, a record of all deviations, violations and serious breaches should be retained within the ISF.

Furthermore, all deviations, violations and/or suspected serious breaches of the protocol and/or GCP should be reported to the Governance Team as soon as possible via the generic R&D inbox: nuth.genericqueries@nhs.net. All associated correspondence should be saved within the ISF.

NuTH Hosted Studies:

For all hosted studies, delivery teams should ensure that all deviations, violations and serious breaches of the protocol and/or GCP should be recorded in the ISF using a deviation log (or equivalent document as provided by the sponsor). All associated correspondence should also be saved, including any notifications to the sponsor and any associated CAPA items.

If a serious breach occurs at NuTH within a hosted study, this should be reported to the sponsor and the NuTH R&D Governance Team as soon as possible via the generic R&D inbox: nuth.genericqueries@nhs.net

6.5 Sponsor Review of Deviations & Violations

For deviations/violations related to high risk NuTH sponsored trials that are submitted to the safety reporting inbox (tnu-tr.safetyreporting@nhs.net), a receipt will be sent by a member of the RCT confirming that the reported incident has been received. This will also include a sponsor review of the event.

The deviation log/violation form and all associated correspondence should also be saved in the SOF.

The RCT will review the deviation/violation to assess:

a) The completeness of the form (or alternative documentation provided)
b) Whether the incident classifies as a serious breach and thus requires expedited reporting to the REC and MHRA (if appropriate) (refer to NJRO-REG-SOP-013: 'Notification of Serious Breaches of Good Clinical Practice or the Trial Protocol').
c) Whether the CAPA items listed are appropriate
d) Advice on other required CAPA items as appropriate

The RCT will sign the violation form (where appropriate) to document their review, and return their comments to the trial management team via email. If the deviation

was submitted in an alternative format (e.g. log / email), then the reviewer will detail their review and any associated feedback via email.

For all studies that fall under the RCT, the RCT will also ensure that the 'Continuous Risk Assessment review' form is completed if any deviations, violations and/or serious breaches are deemed to impact the risk assessment. This is to ensure that changes in risk are documented and appropriate risk mitigation strategies are put in place (refer to NJRO-REG-SOP-004: 'Clinical Trial Risk Assessment for High Risk, NuTH FT Sponsored Trials'). Where the RCT feel that no changes to the risk assessment are required, this will be stated within the sponsor review email to demonstrate that a review has taken place.

All correspondence regarding this review should be saved in the SOF as per the NJRO Document Naming Convention (see NJRO-REG-GUIDE-001: 'SOF Structure Naming Convention').

6.6 Implementing CAPA

Where CAPA items are deemed appropriate by sponsor it is expected that the delegated team (CI/PI, delivery, CTU) will ensure actions are followed-up and concluded.

If an item is added by sponsor and deemed high risk, sponsor will request the delegated team to report back within an agreed time frame for further review. Any such items will require confirmation by sponsor that it is closed.

6.7 Serious Breaches

Where persistent and/or significant deviations occur, these may be classed as a serious breach if the event results in a serious breach of GCP and/or the study protocol.

The judgement regarding whether a 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.

For high risk NuTH sponsored trials, it is the responsibility of the RCT to make a judgement as to whether a potential breach or non-compliance is a 'serious breach' and requires reporting to the competent authority and REC (see NJRO-GEN-SOP-013: 'Notification of Serious Breaches of Good Clinical Practice or the Trial Protocol').

For low-medium risk NuTH sponsored studies, this responsibility falls to the Governance Team.

For further information regarding the process of reporting a Serious Breach to the sponsor, REC and Competent Authority, please see NJRO-GEN-SOP-013: 'Notification of Serious Breaches of Good Clinical Practice or the Trial Protocol'.

6.8 Protocol Waivers

Protocol waivers are prospective deviations or waivers to the protocol. Non-compliances such as these are deemed unacceptable as they constitute a deliberate breach of Regulation 29 of SI 2004/1031:

'Subject to regulation 30 of the SI 2004/1031, no person shall conduct a clinical trial otherwise than in accordance with – (a) the protocol relating to that trial, as may be amended from time to time in accordance with regulations 22 to 25'.

Consequently, protocol waivers **will not** be approved for studies sponsored or hosted by NuTH.

For example, it is unacceptable for a sponsor (or CI on behalf of sponsor) to permit subjects to be included in a trial when they do not meet all of the eligibility criteria defined within the protocol. If a study experiences difficulties in recruitment relating to eligibility criteria, these should be addressed via a substantial amendment if necessary.

NuTH as a hosting site **will not** accept waivers from external sponsors. Delivery teams should report any requests to the NJRO Governance team via: nuth.genericqueries@nhs.net.

6.9 Urgent Safety Measures

Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004: SI 2004/1031 specifies that the sponsor and investigator may take appropriate USM's in order to protect clinical trial participants against any immediate hazard to their health or safety.

USMs can be implemented with immediate effect without needing to gain prior authorisation from the REC, HRA or MHRA (where applicable).

However, any USMs implemented must be notified to the sponsor immediately. For high risk studies sponsored by NuTH, these should be notified to the RCT via the safety reporting inbox (tnu-tr.safetyreporting@nhs.net) or by contacting the RCT directly on 0191 2824457.

For NuTH sponsored high risk trials, investigators, study teams and trial management staff all have a responsibility for notifying the RCT of any USMs that have been implemented.

Reporting USMs in CTIMPs (& studies requiring MHRA Notification)

With regards to USM's relating to a CTIMP, the sponsor (or delegated individual) should immediately (ideally within **24 hours**) telephone the REC that gave the favourable opinion for the trial and the MHRA Clinical Trials Unit (MHRA CTU) to discuss the incident with a safety scientist or medical assessor.

The MHRA will usually request the following information:

- The IRAS ID and/or the EudraCT number of: the trials for which USM action has been taken; other ongoing trials with the same IMPs; and potential trials run by a different Sponsor affected by the USM action.
- The affected IMP(s)
- Nature of the safety concern and whether it has been reported as a SUSAR
- Which USMs have been taken and when
- The number of UK subjects who are currently receiving the IMP, the number of subjects who received it and the number affected by the USM
- Contact details in case of further questions

Where this information is not available during the initial call it should be provided as soon as possible.

After discussing the USM via phone, written notification of the measures taken and discussion with the medical assessor must be submitted to the MHRA within **3 days** from the date the measures were taken. The MHRA will usually provide instruction on how to provide a written report. For trials not approved via Combined Review, the sponsor will usually be instructed to send an email to the medical assessor who assessed the USM over the phone, clintrialhelpline@mhra.gov.uk with 'Urgent Safety Measure' included in the email subject.

However if at least one of the trials covered by the USM has gone through the Combined Review process, then the USM written notification should be submitted via the Integrated Research Application System (IRAS).

Contact details for the relevant REC can be found on the HRA website and details of the MHRA CTU can be located on the MHRA website.

The sponsor (or delegated individual as documented in the Delegation of Duties Agreement) should notify the REC that provided the favourable opinion, HRA and the Competent Authority (MHRA within the UK) within **3 calendar days** of the USM being implemented.

However, if the USM relates to research of a pandemic disease or a serious risk to human health or potentially a serious risk to human health, then the REC, HRA and competent authority must be informed **as soon as possible**.

The submission to the MHRA and REC should include:

- A cover letter (REC Safety Reporting cover sheet – including details of the event, measures taken, reasoning/justification for the measures taken and plans for further action)
- Details of the medical assessor contacted and associated discussions

The REC/MHRA will review such notifications and consider whether the measures taken are appropriate in relation to the apparent risk to subjects and what further action the sponsor and/or Investigator(s) propose to take. Where any concern arises about the safety or welfare of participants or the conduct of the research, these will be addressed with the sponsor/CI.

Notification of a substantial amendment (Amendment tool plus any updated document including the changes agreed with the medical assessor) is also required. The substantial amendment covering the changes made as part of the USM should be submitted within approximately two weeks of notification to the MHRA. Any potential reason for delay to submission of the substantial amendment should be discussed and agreed with the medical assessor at the time of initial notification or through a follow up call.

CTIMPs that have halted due to a USM can only be restarted after receiving approval from the REC, HRA and MHRA.

For high risk NuTH sponsored trials, the RCT are responsible for reporting USMs to the REC, HRA and MHRA, although this may be delegated to a CTU via a Delegation of Duties Agreement.

For non-NuTH Sponsored (hosted) CTIMPs, USMs taken by NuTH staff should be reported to the NJRO Governance Team (in addition to the sponsor) as soon as possible via the generic R&D Inbox (nuth.genericqueries@nhs.net). This

should be followed up via the amendment process but should be implemented immediately as required/instructed by the study sponsor.

For non-NuTH Sponsored (hosted) CTIMPs, NuTH staff wanting to implement an USM should **when possible** first consult the protocol, CI and sponsor as well as the NJRO Governance Team via the generic R&D Inbox (nuth.genericqueries@nhs.net). All decisions should be clearly documented and provided to sponsor and follow up actions should be completed as per study protocol and sponsor requirements.

USMs in Non-CTIMPs

For trials that do not require a clinical trial authorisation or letter of no objection from the MHRA, USMs do not need to be notified to the MHRA.

The sponsor (or delegated individual) should telephone the REC that provided the favourable ethical opinion (ideally within 24 hours) to notify them of the USM.

This should be followed up in writing within **3 calendar days** with a letter setting out the reasons for the USM along with any plans for further action.

Where an USM requires an amendment to the study documentation (e.g. protocol), this should be submitted as a substantial amendment to the REC and HRA as soon as possible. The amendment documentation should highlight that the amendment has been made in response to an USM.

For high risk NuTH sponsored non-CTIMPs (e.g. some surgical intervention trials), the RCT are responsible for reporting USMs to the REC and HRA, although this may be delegated to a CTU (or appropriate delegate) via a Delegation of Sponsor Duties Agreement.

For low/medium risk NuTH sponsored non-CTIMPs, it is the responsibility of the CI with assistance from the NJRO Governance Team to report any USMs to the REC and HRA.

Temporary halt of the trial

If the sponsor and CI decide that the hazard necessitates a temporary halt to the trial (whether this is a halt of the whole trial or at individual sites), the REC and MHRA (if applicable) must be notified **within 15 days** of the halt via a substantial amendment.

It should be clear what specifically has been halted (recruitment or an interruption to the treatment of patients on the study) and the reasoning behind all associated decision making.

Re-starting the trial

If the sponsor has submitted a substantial amendment to halt the trial and subsequently wishes to restart the study if it has been shown safe to do so, this should be done by submitting a further substantial amendment to the REC, HRA and MHRA (where applicable). Supporting evidence should be included within the submission to support that it is now safe to resume the study. The trial should not be restarted until all approvals and permissions have been received.

Study termination

If the sponsor and CI decide not to recommence the temporarily halted trial, the CI (or an appropriate delegate) should submit an End of Trial Declaration to the REC and MHRA **within 15 days** of the decision being made. An explanation of the reasons for early termination should be provided. See NJRO-REG-SOP-003: 'End of Study Procedures' for further information.

A substantial amendment may also be submitted alongside the end of study declaration when it is necessary to seek approval of related actions such as informing subjects and arranging continuing follow up outside of the trial.

7. References

Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical trials for medicines: manage your authorisation, report safety issues. https://www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues#urgent-safety-measures

Medicines and Healthcare Products Regulatory Agency (MHRA) Good Clinical Practice Guide. 2012.

The Medicines for Human Use (Clinical Trials) Regulations 2004; Statutory Instrument 2004; 1031.

Indexed ICH GCP Guidelines with Integrated Addendum E6(R2) Step 4, November 2016.

Key Requirements Affecting Clinical Trials in Europe, Fifth Edition, August 2017.

European Medicines Agency, Q&A: Good Clinical Practice. http://www.ema.europa.eu/

8. Appendices

Appendix 1: NJRO-GEN-T-003 Deviation Log Template
Appendix 2: NJRO-GEN-T-004 Violation Form Template