Identifying and Preventing Non-compliance with Good Clinical Practice or the Protocol Guidance Document

Division: Strategy and Transformation

Specific staff groups to whom this policy directly applies	Likely frequency of use	Other staff who may need to be familiar with policy
Staff employed by North Bristol Trust who directly or indirectly work on Clinical Research within the Trust	Role Dependant	Staff not employed by North Bristol NHS Trust who are working on Research studies sponsored or hosted by NBT

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1. Purpose	The purpose of this Guidance Document is to define non-compliance with ICH Good Clinical Practice (GCP), the approved protocol and applicable regulatory requirements, and to describe the responsibilities of relevant parties in the identification, escalation and management of such non-compliance, in line with the applicable UK clinical trials regulatory framework. Where non-compliance is identified, including breaches of ICH GCP or the approved protocol, the assessment, categorisation and escalation of the issue will be undertaken in accordance with the SOP Managing Breaches of Good Clinical Practice or the Protocol (RD/QMS/SOP012).
2. Key Messages	All research studies at NBT whether they involve clinical trials of investigational medicinal products (CTIMPs) or not must be conducted according to ICH Good Clinical Practice (GCP) standards to protect participants and ensure high-quality, reliable data. Non-compliance with protocols, SOPs, GCP, or regulatory requirements can range from minor to serious, with serious breaches requiring reporting to regulatory authorities. Although non-compliance can occur even in well-run research teams, the risk can be reduced through strong adherence to SOPs, good communication, accurate record-keeping, ongoing monitoring, proper staff training, clear delegation of responsibilities, and voluntary audits by the NBT R&D office. All research studies undertaken at North Bristol NHS Trust (NBT), whether or not they involve clinical trials of investigational medicinal products (CTIMPs), must be conducted in accordance with ICH Good Clinical Practice (GCP), the approved protocol and applicable regulatory requirements, in order to protect the rights, safety and wellbeing of participants and to ensure the generation of high-quality, reliable data. Non-compliance with protocols, SOPs, GCP or regulatory requirements may range in nature and severity from minor deviations to serious or systemic non-compliance. Certain serious breaches remain subject to reporting to regulatory authorities, in accordance with the applicable regulatory framework. While non-compliance may occur even within well-run research teams, the risk can be minimised through effective governance and oversight, including adherence to approved SOPs, clear communication, accurate and contemporaneous documentation, proportionate monitoring, appropriate staff training, robust delegation practices and, where appropriate, audit activity undertaken by the NBT R&D office This guidance document must be applied in accordance with the regulatory framework applicable to the individual study, including transitional arrangements for studies approved prior to the implementation of the Medicines for Human Use (Clinical Trials) Regulations 2025

	Abbreviations **CAPA** Corrective and Preventative Action **CI** Chief Investigator **CTIMP** Clinical trials of Investigational Medicinal Products **ICH GCP** International Conference on Harmonisation Guidelines for Good Clinical Practice **NBT** North Bristol NHS Trust **PI** Principal Investigator **R&D** Research and Development **REC** Research Ethics Committee **MHRA** Medicines and Healthcare Products Regulatory Agency **NBT** North Bristol NHS Trust **SOP** Standard Operating Procedure **Sponsor** The individual, company, institution or organisation which takes on ultimate responsibility for the initiation, management (or arranging the initiation and management) of and/or financing (or arranging the financing) for that research
3. Relevant Policies & Guidance	• Health Research Authority Health Research Authority. UK Policy Framework for Health and Social Care Research. London: Health Research Authority; 2017. • ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R3) • The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (SI 2025/538). **NBT R&D SOP's** RD/QMS/SOP/012 Identifying and Preventing Non-compliance with Good Clinical Practice or the Protocol
4. Operational Areas Included	This SOP is applicable to all research studies sponsored by NBT

5. Operational Areas Excluded	Research Studies that are not sponsored by NBT
6. Who should read this	This SOP should be used by Investigators and other members of the research team involved in research studies sponsored by NBT. Where NBT-sponsored studies are conducted in collaboration with external stakeholders, such as Clinical Trials Units (CTUs), it may be appropriate to adopt external standard operating procedures to support effective project governance and delivery of delegated activities. In such cases, both the external organisation and the NBT Sponsorship Team must ensure that any external SOPs are reviewed and confirmed as being compatible with NBT requirements and the applicable regulatory framework. In the event of a discrepancy or conflict between an external SOP and NBT procedures, the NBT SOP will take precedence, unless a documented exception has been formally agreed by the Research Operations Manager or the Deputy Director of Research.
7. Roles responsible for carrying out this procedure	**Chief and/or Principal Investigator** It is the responsibility of the CI and PI to ensure that the research study is run in accordance with ICH GCP standards and the study protocol that has received regulatory approvals (as applicable). Elements of this responsibility may be delegated to a suitably qualified or experienced member of the research team, overall accountability for compliance remains with the CI and/or PI. All delegated duties must be clearly documented on the study delegation log and reviewed periodically to ensure they remain appropriate. **NBT R&D** NBT R&D is responsible for promoting and enforcing compliance with ICH GCP and applicable regulatory requirements for research studies. Where NBT is the Sponsor, R&D provides sponsor oversight for the identification, assessment, categorisation and escalation of non-compliance, in accordance with Trust SOP's. Where NBT is hosting a study sponsored by another organisation, instances of non-compliance identified at site will be managed in accordance with local Trust procedures and escalated to the Sponsor in line with agreed governance arrangements. To ensure ICH GCP compliance, monitoring of studies taking place at NBT will be carried out in accordance with the specific arrangements made and agreed by the sponsor. In addition, R&D may audit the study as part of their quality assurance procedures. Non-compliance may be identified during these routine monitoring/audit activities.

	All instances of non-compliance identified by research staff must be reported promptly to R&D (and the Sponsor, if NBT are hosting the study). NBT's standard operating procedure for reporting non-compliance is outlined in the SOP on Managing Breaches of Good Clinical Practice or the Protocol (RD/QMS/SOP/012). Any serious breaches of ICH GCP or the approved protocol occurring in NBT sponsored studies will be assessed and handled in line with the procedure outlined in the SOP on Managing Breaches of Good Clinical Practice or the Protocol (RD/QMS/SOP/012).

8. Procedure:

8.1 Background: ICH GCP and Protocol Compliance

CTIMPs are required by law to be run to ICH GCP standards and applicable regulatory requirements. ICH GCP provides an international ethical and scientific quality standard for the design, conduct, recording and reporting of clinical research and is intended to protect the rights, safety and wellbeing of research participants and to ensure the credibility of research data.

While ICH GCP was developed primarily for CTIMPs, its principles are applicable to other types of clinical research where participant safety, data integrity and scientific validity may be affected.

8.2 Research at NBT

It is the policy of North Bristol NHS Trust that all research studies undertaken within the organisation, whether or not they involve a CTIMP, are conducted in accordance with ICH GCP, the approved protocol and applicable regulatory and ethical requirements. This approach supports the protection of research participants, promotes consistent governance standards, and ensures the generation of high quality, reliable research data.

9. Defining Non-Compliance

9.1 What is non-compliance?

According to the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH GCP), non-compliance can be described as:

"Noncompliance with the protocol, Standard Operating Procedures (SOPs), ICH GCP and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff…"

In practice, non-compliance may arise from a single isolated incident or from repeated or systemic failures and may vary in nature and severity. The identification, assessment and management of

non-compliance is essential to protect the rights, safety and wellbeing of research participants and to ensure the reliability and integrity of research data

'Non-compliance' is therefore a broad concept and includes, but is not limited to:

- Research duties undertaken by staff without appropriate experience, training or competency for the activities being performed;
- Failure to ensure roles, responsibilities and delegated duties are clearly defined, documented and maintained throughout the conduct of the research; Undertaking research without obtaining a favourable ethical opinion from an NHS Research Ethics Committee (REC)
- ; Undertaking research without obtaining the required NHS R&D permission or confirmation of capacity and capability from participating organisation
- Undertaking a clinical trial without approval (Clinical Trial Authorisation) from the Medicines and Healthcare products Regulatory Agency (MHRA);
- Failure to conduct the study in accordance with the current approved research protocol;
- Failure to obtain the necessary approval(s) for any modification to the protocol or patient documentation (except in the case of Urgent Safety Measures);
- Failure of the contracted pharmacy unit to maintain complete and accurate records of Investigational Medicinal Products (IMPs);
- Failure of research staff to store, handle or account for IMP in accordance with applicable regulatory requirements;
- Failure to correctly administer IMPs to each participant, including dosing, timing or method of administration as specified in the protocol;
- Failure to obtain informed consent properly and in line with applicable regulatory requirements and current REC-approved consent forms and patient information sheets;
- Coercing or unduly influencing individuals to participate or continue to participate in a research study;
- Deficiencies in the accuracy, completeness, legibility and timeliness of data reported to the Sponsor in Case Report Forms (CRFs) and in all required reports;
- Failure to manage research data securely, in line with applicable legislation, trust policy and good practice standards;
- Improper record-keeping and failure to retain Essential Documents in the Trial Master File and/or Investigator Site File;
- Failure to retain research documentation for the appropriate retention period;
- Failure to submit periodic progress and safety reports to the relevant bodies within the required timelines;
- Failure to record, assess and report Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) in accordance with regulatory requirements;
- Failure to comply with the SOPs of the Sponsor or host institution;
- Failure to submit end of study notifications and final reports to the appropriate regulatory, ethic or other bodies. to provide final reports to the appropriate bodies.

10. Categories of Non-Compliance

The nature, severity and frequency of non-compliances will determine how the deviation is categorized, including whether the issue represents an isolated incident, a recurring issue, or systemic failure (see table below).

The category into which a deviation falls determines the action that should be taken by the sponsor. Further detail on the management, escalation and reporting of non-compliance for NBT sponsored studies is set out in the SOP Managing Breaches of Good Clinical Practice or the Protocol (RD/QMS/SOP012)

Certain instances of non-compliance are classed as 'Serious' and must be reported to the relevant regulatory authorities (see SOP on Managing Breaches of Good Clinical Practice or the Protocol (RI/QMS/SOP012) for details of how this will be managed when NBT are the sponsor).

DEVIATION CATEGORY
Category A: Serious • Significant and unjustified departure(s) for applicable legislative requirements, ICH GCP or the approved protocol with evidence of at least one or more of the following: i) The safety, rights or well-being of trial participants has been or has significant potential to be jeopardised ii) The reliability of scientific validity of the clinical trial data are compromised. iii) There are a number of major non-compliances (as defined in category B) indicating systematic quality assurance failure • Inappropriate, insufficient, or untimely corrective action has taken place regarding previously reported major non-compliances (as defined in category B) • The Trial Master File does not comply with regulatory requirements, is not readily available or accessible, or is incomplete to an extent it impedes regulatory review or obstructs inspection.
Category B: Major • Significant and unjustified departure(s) from applicable legislative requirements, ICH GCP or the approved protocol that may not have developed into a critical issue but may have the potential to do so unless addressed • This includes but is not limited to: • A number of related departures within a single area of responsibility, indicating emerging or localised weaknesses in systems, controls or oversight; • Failures that suggest inadequate implementation of procedures, training or monitoring arrangements. •

Category C: Other

Departures from applicable requirements that are isolated, non-systemic and neither critical nor major in nature, including deviations from:

i) Legislative requirements
ii) ICH GCP guidelines
iii) Procedural requirements
iv) Good clinical practice

11. Preventing Non-Compliance

Non-compliance with ICH GCP, the research protocol or approved regulatory requirements can occur even in well organised and well-trained research teams. Proactive governance, effective oversight and clear role definition are therefore essential to minimise the risk of non-compliance.

The risk can be minimised if the following steps are taken:

- Reading and following the Standard Operating Procedures issued by the NBT R&D office and/or the study sponsor;
- Ensuring good communication between members of the research team and relevant stakeholders;
- Continuous self-monitoring and review of study conduct against the protocol and regulatory requirements
- Maintenance of complete, legible, accurate and contemporaneous study records;
- Ensuring the Delegation of Responsibilities Log in the site file is continually reviewed and updated, if necessary;
- Ensuring that all members of the research team are suitably qualified, trained and experienced for the tasks they undertake, with training documented as appropriate
- Engagement with proportionate monitoring and quality assurance activities, including the option to request audit or advisory support from the NBT R&D Office where risks are identified.