North Bristol NHS Trust

Guidance Document

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

This guidance accompanies SOP RI/QMS/SOP/012 Managing Breaches of Good Clinical Practice or the Protocol

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1.0	18-02-16	Updated references and branding

1. PURPOSE AND SCOPE

The purpose of this Guidance Document is to outline the responsibilities of different parties in identifying and reporting ICH GCP and/or Protocol non-compliance, and how non-compliance is defined.

When breaches of ICH GCP or the approved Protocol are identified, the procedure outlined in the SOP, Managing Breaches of Good Clinical Practice or the Protocol (RI/QMS/SOP012) should be followed.

2. DEFINITIONS/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&I	NBT Research & Innovation Office
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. BACKGROUND: ICH GCP AND PROTOCOL COMPLIANCE

CTIMPs are required by law to be run to ICH GCP standards. The introduction of the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH GCP) notes that, although they are primarily directed towards CTIMPs: 'The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects'.

3.1. Research at NBT

It is the policy of NBT that all research studies, whether a CTIMP or not, should be run to ICH GCP standards for the protection of research participants and in order to ensure consistent practice and scientific quality.

3.2. The role of the 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 and the approved study protocol. Part of this responsibility may be delegated to a

suitably qualified or experienced member of the research team and recorded on the appropriate delegation log.

3.3. **The role of the NBT R&I**

R&I is responsible for promoting and enforcing compliance with ICH GCP. Irrespective of the identity of the Sponsor and subject to any additional procedures a sponsor may have, R&I will be responsible for managing any instances of non-compliance.

To ensure ICH GCP compliance, monitoring of studies taking place at NBT will be carried out in accordance with the specific arrangements made by the sponsor. In addition, R&I may audit the study as part of their quality assurance procedures. Non-compliance may be identified during these routine monitoring/audit activities.

Additionally, instances of non-compliance identified by research staff must be reported to R&I (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 (RI/QMS/SOP012).

Any serious breaches of ICH GCP or the Protocol occurring in NBT sponsored studies will be handled in line with the procedure outlined in the SOP on Managing Breaches of Good Clinical Practice or the Protocol (RI/QMS/SOP012).

4. DEFINING NON-COMPLIANCE

4.1. **What is Non-Compliance?**

According to the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH GCP) paragraph 5.30, non-compliance can be described as:

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

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

- Research duties undertaken by staff without appropriate experience and education;
- Delegation of responsibilities unclear and undocumented throughout conduct of the research;
- Undertaking research without obtaining a favourable ethical opinion from an NHS Research Ethics Committee (REC);
- Undertaking research without obtaining NHS R&D permission from each NHS organisation;
- Undertaking a clinical trial without approval (Clinical Trial Authorisation) from the Medicines and Healthcare products Regulatory Agency (MHRA);
- Failure to comply with the current approved research protocol;

- Failure to obtain the necessary approval(s) for any amendment 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 IMP in accordance with applicable regulatory requirements;
- Failure to correctly administer IMPs to each subject and the intervals set out in the protocol;
- Failure to take informed consent properly and in line with applicable regulatory requirements and REC-approved consent forms and patient information sheets;
- Coercing or unduly influencing patients to participate or continue to participate in a project;
- 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 data securely, in line with applicable legislation 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;
- Failure to record, assess and report Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) in the prescribing format;
- Failure to comply with the SOPs of the Sponsor or host institution;
- Neglecting to provide final reports to the appropriate bodies.

5. CATEGORIES OF NON-COMPLIANCE

The nature and frequency of non-compliance determines how the deviation is categorised (see table below).

The category into which a deviation falls determines the action that should be taken by the sponsor (see SOP on Managing Breaches of Good Clinical Practice or the Protocol (RI/QMS/SOP012) for details of actions that will be taken by R&I for NBT sponsored studies).

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 with evidence of at least one of the following: i) Safety or well-being of trial subjects has been or has significant potential to be jeopardised ii) The clinical trial data are unreliable 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 regulations, is not readily available or accessible, or is incomplete to an extent it impedes or obstructs inspection
CATEGORY B: MAJOR • Significant and unjustified departure from applicable legislative requirements that may not have developed into a critical issue bit may have the potential to do so unless addressed • A number of departures from applicable legislative requirements and/or ICH GCP guidelines within a single area of responsibility, indicating a systematic quality assurance failure
CATEGORY C: OTHER • Departure from one or more of the following has occurred but it is neither critical or major: i) Legislative requirements ii) ICH GCP guidelines iii) Procedural requirements iv) Good clinical practice

6. PREVENTING NON-COMPLIANCE

Non-compliance with ICH GCP or the research protocol can occur even in well organised and well trained research teams. The risk can be minimised if the following steps are taken:

- Reading and following the Standard Operating Procedures issued by the NBT R&I office and/or the study sponsor;
- Ensuring good communication between members of the research team;
- Continuous self-monitoring;
- Complete, legible and accurate record-keeping;
- Ensuring the Delegation of Responsibilities Log in the site file is continually reviewed and updated, if necessary;

- Ensuring all members of the research team are appropriately qualified and experienced for their role in the research;
- Voluntarily requesting that the NBT R&I office undertake an audit of the research.

7. RELATED SOPS AND DOCUMENTS

- Health Research Authority
  UK Policy Framework for Health and Social Care Research
  www.hra.nhs.uk

- ICH Secretariat
  Guidelines for Good Clinical Practice (E6 R2, Step 4, 2016)
  www.ich.org

- The following R&I documents are available on the NBT website: http://www.nbt.nhs.uk/research

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