Managing Breaches of Good Clinical Practice or the Protocol

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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Date of Approval:	07th April 2026
Next Review Due:	07th April 2029
Version:	RD/QMS/SOP/012 – Version 2.2
KEYWORDS:	Protocol Deviation, Protocol Breaches, Category A, B and C, Serious Breaches. Reporting to Regulatory Authorities, Reporting timelines, Delegation of Responsibilities, R&D Non-Compliance Panel
Summary of changes since the previous version	Clarification of categorisation of protocol deviations. Changed format to align with NBT SOP template Changed R&I to R&D Change the naming convention of R&D SOP's Added information in relation to responsibilities when working with Clinical Trials Units.

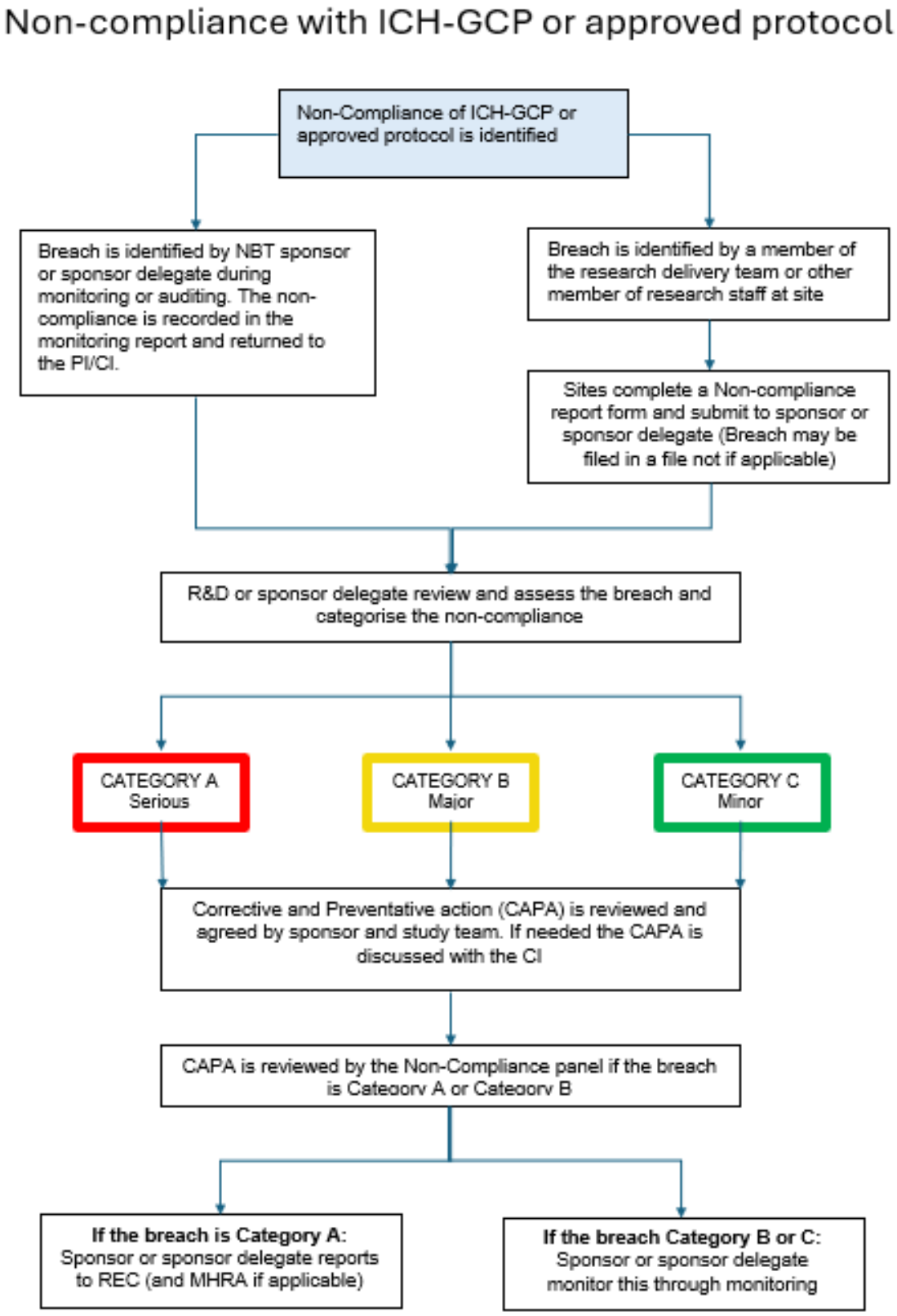
	Regulatory and ICH GCP references updated to align with The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (SI 2025/538) and latest ICH GCP E6 (R3) General editorial improvements have been applied throughout the SOP to enhance readability and improve the overall flow of content

1. Purpose	The purpose of this SOP is to outline the procedure to be followed when a breach of Good Clinical Practice or the approved protocol is identified in trials sponsored by NBT. The focus of this SOP is CTIMPS, however the standards described should be applied to ALL research studies.
2. Key Messages	This SOP outlines the actions to be taken when a breach of Good Clinical Practice (GCP), the approved protocol, or applicable regulatory requirements is identified and assessed as serious. Under the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, a *serious breach* is defined as a breach that is likely to have a significant impact on either: • The safety or physical or mental integrity of the subjects; or • The scientific value of the trial. This SOP applies to clinical trials sponsored by North Bristol NHS Trust. For externally sponsored studies hosted by the Trust, the external Sponsor's breach management procedures should be followed. However, the Trust's Research & Development (R&D) department must still be notified of any suspected serious breach. The Principal Investigator at North Bristol NHS Trust is responsible for ensuring that R&D is informed of the Sponsor's assessment and confirmation of any suspected serious breach as soon as this determination has been made Clinical Trials of Investigational Medicinal Products (CTIMPs) must be conducted in accordance with the principles of ICH Good Clinical Practice. In line with the 2025 regulatory framework and ICH GCP E6(R3), sponsors are expected to implement proportionate, risk-based oversight and to identify, assess, document, and address noncompliance in a timely manner. Further guidance on identifying, assessing, and preventing noncompliance with ICH

	GCP or the approved protocol is provided in Identifying and Preventing Noncompliance with Good Clinical Practice or the Protocol (RD/QMS/SOP012b), available on the R&D website. This SOP applies to all Trust sponsored and hosted clinical trials and should be applied in accordance with the regulatory framework applicable to the individual study, including transitional arrangements for trials approved prior to 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 **CTU** – Clinical Trials Unit **ICH GCP** – International Conference on Harmonisation Guidelines for Good Clinical Practice **NBT** – North Bristol NHS Trust **PI** – Principal Investigator **R&D** – NBT Research & Innovation Office **R&D Non-compliance Panel** – Clinical Trials Manager, Clinical Trials Officer and Research Operations Manager. The group may convene via full meeting or viaEmail **REC** –Research Ethics Committee **MHRA** –Medicines and Healthcare Products Regulatory Agency **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. UK Policy Framework for Health and Social Care Research. London: Health Research Authority; 2017. • ICH Harmonised Tripartite Guideline for Good Clinical Practice E6 (R3) • Medicines and Healthcare products Regulatory Agency *Guidance on Serious Breaches of GCP or the Protocol* • 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).

	The following R&I documents are available on the NBT website: www.nbt.nhs.ukRD/QMS/TMPL/SOP/012a - ICH GCP & Protocol Non-compliance Report Form RD/QMS/TMPL/SOP/012b - Identifying and Preventing Non-compliance with Good Clinical Practice or the Protocol RD/QMS/TMPL/SOP/012c - Protocol Deviation Review and Analysis Form
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 applies to all investigators, trial managers, CTUs and research team members involved in studies sponsored by NBT.
7. Roles responsible for carrying out this procedure	**Chief Investigator (CI)** • Oversees protocol compliance across all sites. • Reviews deviation patterns and supports assessment of impact. • Coordinates corrective actions across the trial. • Advises on escalation and works with sponsor on serious breaches. **Sponsor** • Holds ultimate legal responsibility. • Defines deviation processes and ensures proper documentation. • Reviews deviations and determines serious breaches. • Reports serious breaches to MHRA/REC. • Ensures monitoring, compliance, and corrective actions.

8. Procedure:


Non-compliance with ICH-GCP or approved protocol
Non-Compliance of ICH-GCP or approved protocol is identified
Breach is identified by NBT sponsor or sponsor delegate during monitoring or auditing. The non-compliance is recorded in the monitoring report and returned to the PI/CI.
Breach is identified by a member of the research delivery team or other member of research staff at site
Sites complete a Non-compliance report form and submit to sponsor or sponsor delegate (Breach may be filed in a file not if applicable)
R&D or sponsor delegate review and assess the breach and categorise the non-compliance
CATEGORY A Serious
CATEGORY B Major
CATEGORY C Minor
Corrective and Preventative action (CAPA) is reviewed and agreed by sponsor and study team. If needed the CAPA is discussed with the CI
CAPA is reviewed by the Non-Compliance panel if the breach is Category A or Category B
If the breach is Category A: Sponsor or sponsor delegate reports to REC (and MHRA if applicable)
If the breach Category B or C: Sponsor or sponsor delegate monitor this through monitoring

8.1 Identifying non-compliance with ICH GCP or the Protocol

A research protocol that has received a favourable ethical opinion and, where applicable, regulatory authorisation, is a controlled document that defines the permitted and non-permitted activities within a clinical trial. Compliance with the approved protocol is essential to safeguard the rights, safety and wellbeing of participants and to ensure the reliability and scientific value of the trial data. This is particularly critical for trials conducted under the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, which place legal obligations on the Sponsor to ensure appropriate oversight and control of trial conduct.

The Chief Investigator (CI) and Principal Investigator (PI) at each site are responsible for ensuring that the trial is conducted in accordance with the approved protocol, ICH Good Clinical Practice (GCP), and applicable regulatory requirements. Research & Development (R&D), acting on behalf of the Trust as Sponsor, is responsible for providing oversight, promoting compliance, and ensuring that systems are in place to identify, assess, and manage non-compliance in a timely and proportionate manner.

For the purposes of this SOP, the term **non-compliance** is used as an umbrella term and may include protocol deviations, protocol violations, or system-level failures to comply with ICH GCP, the approved protocol, or regulatory requirements. While these terms may differ operationally, they are collectively governed by the processes described in this SOP.

In line with the 2025 regulatory framework and ICH GCP E6(R3), non-compliance may be identified through both proactive and reactive oversight mechanisms, including, but not limited to:

(a) reported directly to R&D by any member of the research or clinical care team;
(b) reported to R&D by the trial manager, including where identification and reporting of noncompliance has been delegated to a Clinical Trials Unit (CTU) on behalf of the Sponsor;
(c) identified through sponsor oversight activities, including monitoring conducted in accordance with the trial's risk-based monitoring and oversight arrangements;
(d) identified during audit or quality assurance activities conducted by or on behalf of R&D.

8.2 Documentation and reporting of breaches

When identified, **ALL** instance of non-compliance of ICH GCP, the approved protocol, or applicable regulatory requirements must be clearly and consistently documented, for example in file notes or ICH GCP & Protocol Non-compliance Report Form (RD/QMS/SOP/012a), in order for appropriate corrective and preventative actions to be agreed and actioned.

All breaches **MUST** also be reported to the sponsor using the ICH GCP & Protocol Non-compliance Report Form (RD/QMS/SOP/TMPL/012a), which is available on the R&D website.

Documentation of a breach will include as a minimum:

(a) A clear description of the non-compliance, including what occurred and how it was identified.

(b) The date and time of its occurrence and the date it was identified.

(c)The site/location where the non-compliance occurred.

(d)Name of PI at site/location.

(e)Immediate actions taken to protect participants and/or data integrity (where applicable)

(f) Corrective and preventative actions taken or planned (i.e. a CAPA plan).

(g) Assessment by the CI or PI (or delegated individual) as to whether the breach affects to a significant degree the safety or physical or mental integrity of the subjects, or the scientific value of the trial, as a whole.

8.3 Categorisation of non-compliance with ICH GCP or the Protocol

Once reported to R&D, each instance of non-compliance will be reviewed and assessed against the grading categories in the table below. Categorisation will be informed by the nature of the non-compliance, its actually or potential impact on participant safety, rights and well-being, data integrity, and the extent which it indicates an isolated event or a systemic failure.

Any issues raised or identified which fall within Category A will be regarded as meeting the regulatory definition of a serious breach, and the procedure outlined in **section 8.4 Managing Serious Breaches** of this SOP will apply. The Sponsor will document their review process in a Protocol Deviation Review and Analysis Form (RD/QMS/TMPL/SOP/012c) where it poses a serious or potentially serious breach.

In line with the principles of risk-based trial management and ICH GCP E6(R3), the Sponsor, in collaboration with the Chief Investigator and research team, will assess all serious breaches and consider whether:

- a review or update of the trial risk assessment or monitoring strategy is required;
- additional corrective and preventative actions are necessary; and
- a substantial modification or other regulatory action should be submitted.

Repeated instances of Category B or Category C non-compliance, or emerging patterns or trends, must also be reviewed to determine whether they collectively indicate a systemic issue that warrants escalation, re-categorisation, or further regulatory action.

DEVIATION CATEGORY	ACTIONS IF BREACH IDENTIFIED DURING MONITORING/AUDIT	ACTIONS IF BREACH REPORTED BY RESEARCH STAFF
CATEGORY A: SERIOUS • Significant and unjustified departure from 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 may not have developed into a critical issue but may have the potential to do so unless addressed and rectified.	The monitor or auditor will identify these issues during monitoring/audit and agree Corrective and Preventative Actions (CAPAs) to be taken. The monitor/auditor will escalate findings to the Research Operations Manager during the visit or as soon as possible following the visit. The non-compliance issue will be logged on an *'ICH GCP & Protocol Non-compliance Report Form'* and the findings will be provisionally graded within **3 working days** after preliminary analysis. The visit report and form will be jointly reviewed by the 'R&D Non-compliance Panel' comprising of Research Compliance Manager, Clinical Trials Officer, and Research Operations Manager to discuss any further investigations required. An R&D Protocol Deviation Review and Analysis Form (RD/QMS/TMPL/SOP/012c) will be completed as part of the review process. Based on the outcome of this review, members of the R&D Non-compliance Panel will determine the next appropriate action which could include: (i) The findings should be regarded as category C and handled accordingly (ii) Additional CAPAs should be implemented (iii) Recruitment should be temporarily halted until issues are resolved (iv) The research should be suspended	Details of the breach will be escalated to the 'R&D Non-compliance Panel' and the same procedures followed as for non-compliance identified during monitoring or audit.

• Significant and unjustified departure from the approved protocol that may have not developed in to a critical issue but may have the potential to do so unless addressed and rectified. • 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. • Repeated or trending Category B non-compliances must be reviewed by the Sponsor to determine whether they collectively meet the definition of a serious breach or require escalation	(v) The research should be terminated Complex cases will be escalated to the Deputy Director of Research. All category A deviations in NBT sponsored trials will be reported to the relevant regulatory authorities in accordance with **section 8.4** of this SOP.	
CATEGORY C: MINOR Departure from one or more of the following has occurred but it is neither critical nor major: • Legislative requirements • ICH GCP guidelines • Procedural and protocol requirements • Good clinical practice Category C non-compliances will be periodically reviewed to identify trends or recurring issues that may indicate emerging risks or systemic weaknesses	Appropriate CAPAs will be identified. These will be documented in a monitoring report sent to the PI of the relevant site (and CI where necessary). The individual responsible for implementing the CAPAs will be identified and all reports retained on the Trial Master File/Investigator Site File.	R&D will discuss the issue with the PI of the relevant site (and CI where necessary) and appropriate CAPAs will be identified, documented and actioned.

8.4 Managing Serious Breaches of ICH GCP or the Protocol

A “serious” breach is a particularly significant matter for CTIMPs because there are specific legal obligations for sponsors to identify, assess and report them.

(a) Reporting Requirements

The Sponsor is responsible for confirming whether a non-compliance meets the definition of a serious breach, documenting the rationale for the decision, and ensuring appropriate escalation and reporting to the relevant bodies.

i. Serious breaches of CTIMPs should be reported to the REC and to the MHRA.
ii. Serious breaches of non-CTIMP studies should be reported to the REC.

(b) Reporting to MHRA

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, require the sponsor of a CTIMP to notify the MHRA in writing of any serious breach of the conditions and principles of ICH GCP or the approved protocol within **7 days** of becoming aware of the breach. In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Sponsor of a CTIMP must notify the MHRA in writing of any serious breach of the conditions and principles of ICH GCP or the approved protocol within 7 days of becoming aware of the breach. Reports must be submitted in line with current MHRA guidance on serious breaches. published on the MHRA website (www.gov.uk).

The MHRA notification should include sufficient information to describe the breach, the actual or potential impact on participant safety and/or scientific value, immediate actions taken, and the proposed corrective and preventative actions (CAPA). Where complete information is not available at the time of initial reporting, the Sponsor should submit follow-up information to the MHRA as it becomes available.

Upon receipt of a CTIMP serious breach notification, the MHRA will log and review it and may take any number of actions depending on the nature of the breach and its potential impact. These are detailed in the MHRA Guidance on Serious Breaches

Please note serious breach events must be referenced within all relevant publications pertaining to the study. The MHRA undertake audits to ensure publication transparency.

(c) Reporting to REC

REC should be informed of any serious breach within **7 days** of the Sponsor becoming aware of the breach. Details reported to REC should include:

i. When the breach occurred.
ii. Where the breach occurred (site/location)
iii. Who was involved.
iv. The outcome and current status

v. Any information provided to participants (where applicable)

vi. An explanation of what happened and why

vii. Immediate actions taken and further action the sponsor plans to take.

viii. If the study is a CTIMP, a copy of the MHRA report form should be included.

In line with risk-based trial management, the Sponsor, in collaboration with the Chief Investigator and relevant trial teams, must consider whether the serious breach indicates a systemic issue requiring review of the trial risk assessment, monitoring/oversight arrangements, training, and/or the need for a substantial modification

8.5 Delegation of Responsibility to External Clinical Trials Unit

Where a study sponsored by North Bristol NHS Trust is managed in whole or in part by an external Clinical Trials Unit (CTU), and it has been agreed that the CTU's procedures for managing breaches will be followed, these arrangements must be clearly defined and documented within the relevant collaboration or delegation agreements.

Operational responsibilities delegated to a CTU may include the identification, documentation and initial assessment of non-compliance, including identifying those breaches that require prompt escalation to the Sponsor. Any suspected serious breach must be notified to the Sponsor without undue delay to enable timely assessment and, where required, regulatory reporting.

Where NBT is Sponsor, reporting of serious breaches to the MHRA will be undertaken by R&D or by a formally delegated CTU representative, as specified in the Roles and Responsibilities section of the collaboration agreement. The Sponsor will ensure there is a clear audit trail documenting decision making, delegation, and confirmation of regulatory reporting responsibilities.

Notwithstanding any delegation, North Bristol NHS Trust, as Sponsor, retains ultimate responsibility for the assessment, classification and reporting of serious breaches in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025.

9. Dissemination and Training:

SOPs will be distributed in accordance with the SOP on Preparation of Research SOPs (RD/QMS/SOP/001).

This SOP and any associated templates and forms will be uploaded to the Trust website (www.nbt.nhs.uk/research) and LEARN on the Trust intranet shortly after having been released.

All staff whose activities are subject to this SOP should ensure that they read and understand the content of this SOP.

The training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the content of this SOP.