North Bristol NHS Trust

Standard Operating Procedure

Managing Breaches of Good Clinical Practice or the Protocol

REFERENCE:	RI/QMS/SOP/012
VERSION NUMBER:	2.1
EFFECTIVE DATE:	28-03-18
REVIEW DATE:	28-03-20
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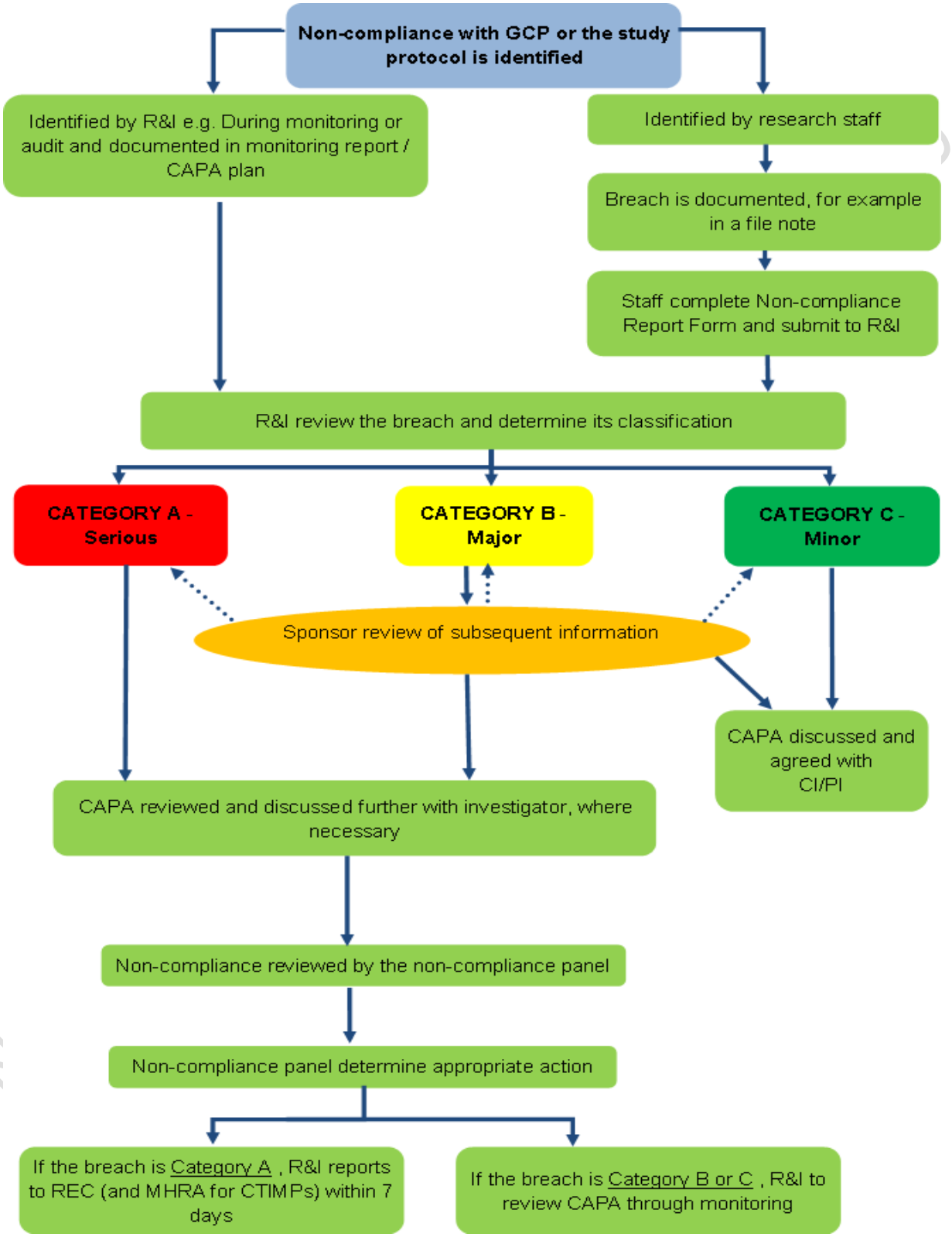
Document Version History

VERSION NUMBER	EFFECTIVE DATE	REASON FOR CHANGE
1.0	01-04-11	SOP renamed, updated in line with new template and recoded from ISOP-C05
2.0	18-02-18	Clarification of R&I process for reviewing breaches and use of *Protocol Deviation Review and Analysis Form*

DO NOT USE THIS SOP IN PRINTED FORM WITHOUT CHECKING IT IS THE LATEST VERSION

Current versions of all Research & Innovation SOPs and accompanying documents are available online. If you are reading this document in printed form, please check that the version number and date match the most recent version on the Research & Innovation website: www.nbt.nhs.uk/research

i. SOP Flowchart



1. PURPOSE AND SCOPE

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.

The SOP also outlines the actions that should be taken when a breach is classified as 'serious'. The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, defines 'serious breach' as a breach that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects; or
- The scientific value of the trial.

This SOP does not cover externally sponsored studies that are hosted by NBT; in which case the Sponsor's own SOPs apply. However, for such studies, R&I must still be notified of the suspected serious breach. The PI at NBT will be responsible for ensuring that R&I is notified of the Sponsor assessment of the reported suspected serious breach as soon as this is confirmed.

CTIMPs are required by law to be run to ICH GCP standards. Guidance relating to the definition and occurrence of non-compliance with ICH GCP or the approved study protocol is provided in Guidance Document: Identifying and Preventing Non-compliance with Good Clinical Practice or the Protocol (RI/QMS/SOP012b), which is available on the R&I website.

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
R&I Non-compliance Panel	Group comprising of two or more of the Research Matron, Clinical Trials Manager, Clinical Trials Officer and Research Operations Manager. The group may convene via full meeting or via email
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. WHO SHOULD USE THIS SOP

This SOP applies to all investigators and research team members involved in studies sponsored by NBT.

4. WHEN SHOULD THIS SOP BE USED

This SOP should be referred to where a breach of ICH GCP or the approved study protocol is identified in a research study sponsored by NBT.

5. PROCEDURE

5.1. Identifying non-compliance with ICH GCP or the Protocol

It is the responsibility of the CI and PI at each site to ensure that the research study is run in accordance with ICH GCP and the approved study protocol. R&I is responsible for promoting and enforcing compliance.

Non-compliance may be identified in several ways, for example:

(a) Reported by any member of staff to R&I.

(b) Identified during monitoring of studies taking place at NBT that is carried out in accordance with specific arrangements made by the study sponsor.

(c) Identified during audit of the study by R&I.

5.2. Documentation and reporting of breaches

When identified, ALL breaches of ICH GCP or the protocol must be clearly and systematically documented, for example in file notes or ICH GCP & Protocol Non-compliance Report Form (RI/QMS/SOP/012a), in order for appropriate corrective and preventative actions to be taken.

When identified, breaches should also be reported to R&I using the ICH GCP & Protocol Non-compliance Report Form (RI/QMS/SOP/012a), which is available on the R&I website.

Documentation of a breach will include as a minimum:

(a) Full details of the breach.

(b) The date and time of its occurrence.

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

(d) 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.

5.3. **Categorisation of non-compliance with ICH GCP or the Protocol**

Once received by R&I, breaches will be considered against the grading categories in the table below. Any issues raised or identified which fall within Category A will automatically amount to a “serious” breach and the procedure outlined in **section 5.4** of this SOP will apply. The Sponsor will document their review process in a Protocol Deviation Review and Analysis Form (RI/QMS/SOP/012c) where it poses a serious or potentially serious breach.

The Sponsor and research team should review breaches and consider whether a review of the risk assessment and/or amendment submission is required. This should be for all serious breaches or when a pattern appears to develop.

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.	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 finding will be provisionally graded within **3 working days** after preliminary analysis. The visit report and form will be jointly reviewed by the 'R&I Non-compliance Panel' comprising of two or more of the Research Matron, Clinical Trials Manager, Clinical Trials Officer, and Research Operations Manager to discuss any further investigations required. An R&I Protocol Deviation Review and Analysis Form (RI/QMS/SOP/012c) will be completed as part of the review process. Based on the outcome of this review, members of the R&I 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 (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	Details of the breach will be escalated to the 'R&I Non-compliance Panel' and the same procedures followed as for non-compliance identified during monitoring or audit.
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.		

	reported to the relevant regulatory authorities in accordance with **section 5.4** of this SOP.	
CATEGORY C: MINOR • 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	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&I will discuss the issue with the PI of the relevant site (and CI where necessary) and appropriate CAPAs will be identified and documented.

5.4 **Managing Serious Breaches of ICH GCP or the Protocol**

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

(a) Reporting Requirements

The sponsor is responsible for reporting serious breaches to the relevant regulatory 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. Breaches should be notified in line with MHRA Guidance on Serious Breaches published on the MHRA website (www.gov.uk).

Where NBT is sponsor, R&I will be responsible for reporting to the MHRA.

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 (see section 5).

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. The location.

iii. Who was involved.

iv. The outcome.

v. Any information given to participants.

vi. An explanation.

vii. What further action the sponsor plans to take.

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

Where NBT is sponsor, R&I will be responsible for reporting to the REC.

6 DISSEMINATION AND TRAINING

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

This SOP and any associated templates and forms will be uploaded to the Trust website (www.nbt.nhs.uk/research) and the Managed Learning Environment (MLE) system 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.

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

- Medicines and Healthcare products Regulatory Agency
  Guidance on Serious Breaches of GCP or the Protocol
  www.gov.uk

- UK Government
  Medicines for Human Use (Clinical Trials) Regulations 2004
  www.legislation.gov.uk

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

RI/QMS/SOP/012a	ICH GCP & Protocol Non-compliance Report Form
RI/QMS/SOP/012b	Identifying and Preventing Non-compliance with Good Clinical Practice or the Protocol
RI/QMS/SOP/012c	Protocol Deviation Review and Analysis Form