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Pharmacovigilance 04 Non-compliance and Serious Breaches

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the Research & Development Webpage for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded version are promptly withdrawn from use unless notified otherwise by the SOP Controller.

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SOP reference:	R&D SOP Ph 04	
Version:	2.0	
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Reviewed by Associate Director of R&D	Julie Hapeshi 27/03/2018	signature
Implementation date of current version:	31 / 03 /2018	
Date of Review:	01 / 01 /2020	

The Gloucestershire Hospitals NHS Foundation Trust wishes to acknowledge York Hospitals NHS Foundation Trust and University Hospitals Bristol NHS Foundation Trust who gave permission to use their templates in the development of these SOPs.

Version History Log

This area will be updated with details of all changes made to the SOP whether due for full review or not.

Version	Details of Change	Date Implemented
1.0	Original SOP	30/01/2015
2.0	Rebranding to GHNHSFT, updating of contact details and reference documents addition of flowchart	31/03/2018

This SOP will be reviewed every two years unless changes to any relevant legislation require otherwise

Contents

1 Introduction, Background and Purpose

Deviations from clinical trial protocols and GCP occur commonly in clinical trials. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. These cases should be documented (for example, in the trial case report form, the Trial Master File and Investigator Site File) in order for appropriate corrective and preventative actions to be taken. In addition, these deviations should be included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data. However, not every deviation from the protocol needs to be reported to the MHRA as a serious breach.

This SOP also outlines the actions that should be taken when a non-compliance episode or serious breach is identified in trials sponsored by the Trust (as defined in The Medicines for Human Use (Clinical Trials) Regulations 2004, regulation 29A of S12004-1031as amended).

The focus of this SOP is CTIMPs however the standards described should be applied to all research studies.

This SOP does not cover externally sponsored studies that are hosted by the Trust; in which case the Sponsor's own SOPs apply. However, for such studies, the Trust R&D Department must still be notified of the suspected serious breach.

The Principal Investigator (PI) at the Trust will be responsible for ensuring that Trust R&D Department is notified of the Sponsor assessment of the reported suspected serious breach as soon as this is confirmed.

2 Who should use this SOP

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

3 When this SOP should be used

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

4. Defining non-compliance and serious breaches

4.1. What is a 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 HRA/ 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

4.2 What is a serious breach?

A '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.

Examples given in the MHRA guidelines are:

- Fraud relating to clinical trial records or data.
  - If the fraud is likely to have a significant impact on the integrity of trial subjects or the scientific value of the data, this will be a serious breach.
- A breach of GCP or the protocol leading to the death, hospitalisation or permanent disability of a trial subject in the UK.
  - Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) resulting from a breach of the conditions and principles of GCP or a breach of the protocol, will constitute a serious breach. However, it should be noted that not every SAE or SUSAR would routinely be classified as a serious breach.
- A failure to report adverse events, serious adverse events or SUSARs in accordance with the legislation.
  - If this failure results in trial subjects, or the public, in the UK being put at significant risk, then this will constitute a serious breach, for example, inadequate safety reporting in dose escalation studies may impact on the decision to escalate to the next dose level.
- Persistent or systematic non-compliance with GCP or the protocol
  - If this non-compliance has a significant impact on the integrity of trial subjects in the UK or on the scientific value of the trial, this will constitute a serious breach. For example, widespread and uncontrolled use of protocol waivers affecting eligibility criteria, which leads to harm to trial subjects in the UK or which has a significant impact on the scientific value of the trial. Another example would be an investigator repeatedly failing to reduce or stop the dose of

an IMP in response to a trigger defined in the protocol (for example, abnormal laboratory results).

- A failure to control investigational medicinal product(s)
  - This will constitute a serious breach if the failure results in trial subjects or the public, in the UK being put at significant risk or the scientific value of the trial being compromised. If a serious breach occurs due to an IMP defect, a drug defect report may need to be submitted to the MHRA Defective Medicines Reporting Centre (DMRC), in addition to the serious breach notification.

It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the trial. If there is any uncertainty then the Sponsor should contact the MHRA for advice at the earliest opportunity.

5. Procedure

It is the responsibility of the Chief Investigator (CI) and Principal Investigator (PI) at each site to ensure that the research study is run in accordance with ICH GCP and the approved study protocol.

The Trust R&D Department is responsible for promoting and enforcing compliance.

5.1. Documentation and reporting of breaches

As soon as a breach has been identified (within 24 hours), the Trust R&D Department must be contacted to assist with the investigation, reporting and outcome. Documentation of a breach will include as a minimum:

i. Full details of the breach.
ii. The date and time of its occurrence.
iii. Any corrective and preventative actions taken or planned (i.e. a Corrective Action Preventive Action (CAPA) Plan).
iv. 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.

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

Once received by the Trust R&D Department, breaches will be considered against the grading categories in the table in Appendix 1. Any issues raised or identified which fall within Category A will automatically amount to a "serious" breach and the procedure outlined in the table in Appendix 1.

5.3 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 at: https://www.gov.uk/good-clinical-practice-for-clinical-trials

Where the Trust is the Sponsor, the Trust R&D Department 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).

(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 the Trust is the Sponsor, the R&D Department will be responsible for reporting to the REC.

6. Other SOPs and documents

Department of Health
Research Governance Framework for Health & Social Care, 2nd Edition, April 2005
www.dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/dh_4108962
 ICH Secretariat

Guidelines for Good Clinical Practice (GCP) (E6 R1 Step 4, 1996)
www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
 Medicines and Healthcare products Regulatory Agency

Guidance on Serious Breaches of GCP or the Protocol
www.gov.uk/government/uploads/system/uploads/attachment_data/file/404588/GCP_serious_breaches_guide.pdf
 UK Government

Medicines for Human Use (Clinical Trials) Regulations 2004
www.legislation.gov.uk/uksi/2004/1031/contents/made

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 Trust R&D Department during the visit, or as soon as possible following the visit. The non-compliance issue will be logged 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 Associate Director Of Research, Senior Research Manager, Lead Research Nurse to discuss any further investigations required. Based on the outcome of this review by the senior staff will determine whether: (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 All 'category A' deviations in Trust sponsored trials will be reported to the relevant regulatory authorities in accordance with **section 5.4** of this SOP.	Details of the breach will be escalated to the Trust R&D Department's senior team and the same procedures followed as for non-compliance identified during a monitoring visit 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		
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 in the Trial Master file/ Investigator Site File.	R&D will discuss the issue with the PI of the relevant site (and the CI where necessary) and appropriate CAPAs will be identified and documented.

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Appendix 2
Flowchart