Standard Operating Procedure CCTU/SOP018

Handling of Protocol and Regulatory Non-Compliance in Clinical Trials

1. Scope

For use by research personnel within the Trust (either as substantive employees or under an honorary contract) involved with, or working on Cambridge Sponsored Clinical Trials of Investigational Medicinal Products.

2. Purpose

To document procedures that will ensure appropriate action is taken for identifying and handling cases of non-compliance with the trial protocol, Standard Operating Procedures or regulatory requirements for:

1. The protection of patients
2. Maintenance of trial integrity
3. Compliance with legal requirements

Compliance with applicable regulatory guidance

To determine the nature and extent of the non-compliance, and to ensure that appropriate documentation, assessment and reporting procedures are followed. This includes discovery of a course of action or event, which may constitute a non-reportable non-compliance (Type I), a reportable minor non-compliance (Type 2) or a major non-compliance/potential serious breach (Type 3) from the approved protocol or regulatory requirements.

3. Definitions and Abbreviations

The headings below contain the definitions of terms and meaning of abbreviations used within the document.

3.1. Definitions

Term	Definition
Cambridge Sponsored	Sponsored by Cambridge University Hospitals NHS Foundation Trust (CUH); or the University of Cambridge (UoC); or jointly by CUH and UoC or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Waiver	Prospective deviation or waiver to the protocol, these types of non-compliances are not acceptable as they constitute a deliberate breach of Regulation 29 of SI 2004/1031. Waivers are also sometimes known as protocol exemptions or authorisations.

Non-Reportable Non-Compliance (Type 1)	Departure from the precise wording of the protocol, SOP or regulatory requirements that has been identified retrospectively and has minimal impact on the integrity of the trial. Examples may include: Missed routine sample collections Data collection outside of visit windows Participant-derived non-compliances (e.g. refusal/forgetting to take medication, failure to attend a scheduled visit) Failure of subject to complete a patient reported outcome questionnaire, providing the data is not a primary end point
Reportable Minor Non-Compliance (Type 2)	Departure from the protocol, SOP or regulatory requirements that has been identified retrospectively and, is not likely to effect to a significant degree: The safety, or physical or mental integrity of the trial subject The scientific value of the trial Examples may include: Missed IMP treatment where treatment is administered by - trial/site staff Eligibility criteria non-compliances Deviations in dosing of non-IMPs Repeated instances of non-reportable non-compliances
Reportable Major Non-Compliance/ potential Serious Breach (Type 3)	Departure from the protocol, SOP or regulatory requirements which is likely to effect to a significant degree: The safety, or physical or mental integrity of the trial subject The scientific value of the trial

3.2. Abbreviations

Abbreviation	Meaning
CCTU	Cambridge Clinical Trials Unit
SOP	Standard Operating Procedure
MHRA	Medicine and Healthcare Products Regulatory Agency
NCF	Non-Compliance Form
CI	Chief Investigator
PI	Principal Investigator
CTC	Clinical Trial Coordinator
TMF	Trial Master File
ISF	Investigator Site File

4. Undertaken by

The CI and/or PI or their delegates who have a responsibility to comply with this SOP.

5. Items Required

- CCTU/FRM013 Non-Compliance Report Form
- CCTU/FRM042 Non-Compliance Log

- CCTU/SOP019 Urgent Safety Measures

6. Summary of Significant Changes

Addition of a 'non-reportable' category of non-compliance, updated clarification of all non-compliance categories, reference to the new document 'Non-Compliance Log' and update to the non-compliance decision-making and recording process.

7. Method

The following sections provide a description of the processes to be followed when implementing this document's procedures.

7.1. Restrictions

There can be no exemptions to compliance with eligibility criteria listed in the current approved protocol. All eligibility criteria non compliances are reportable.

7.2. Procedure once an episode of Non-Compliance is suspected

- If a non-compliance is suspected further information must be obtained concerning the nature and extent of the episode
- A decision will be made by the trial coordination team in consultation with the Regulatory team as necessary whether the non-compliance is reportable or non-reportable (see 3.1 Definitions)

7.2.1. Non-reportable non-compliances

Where an episode is considered to be non-reportable, it should be entered into the Non-Compliance Log (CCTU/FRM042). Where this is a non compliance at the site discovered by the coordination team the site team should be informed in order to prevent future occurrences of the incidence.

7.2.2. Reportable non-compliances

Where an episode is considered to be reportable a Non-Compliance Report Form (CCTU/FRM013) should be completed and the Protocol Non-Compliance Log (CCTU/FRM042) populated.

- Where necessary members of CCTU can complete the NCF, otherwise a member of the trial team must:
    - Complete/review the NCF ensuring full details of the episode and any corrective and preventative actions taken are provided (advice can be sought from the regulatory team on appropriate corrective and preventative action)
    - Inform the CI and if applicable, the involved site PI of the non-compliance and ensure that they add further comments and explanatory notes if appropriate
- The NCF must be signed by the CI and if applicable, the involved site PI.
- The non-compliance should initially be assessed and categorised by the CI as either:

  - A non-compliance (Type 2)
  - A potential serious breach (Type 3)
- In all cases sufficient assessment of the episode must be given by the CI in order to justify its categorisation
- A copy of the NCF must be provided to the CCTU Regulatory Team for initial Sponsor categorisation
- In instances where the Sponsor categorisation differs from the CI categorisation, discussions seeking agreement for the categorisation should be undertaken however, if no agreement can be reached the Sponsor categorisation will be considered as definitive and will be escalated or closed as appropriate
- If urgent safety measures are required they must be carried out as soon as possible and fully documented, refer to CCTU/SOP019 Urgent Safety Measures
- The definitive NCF signed by PI (where applicable), CI and the sponsor representative should be filed in the sponsor file, TMF and ISF if applicable.

7.2.3 Reviewing non-compliances

The Non-Compliance Log should be periodically reviewed by both the monitor (in trials where a monitor has been assigned) to confirm the categorisation, and by the trial management teams to look for patterns or trends which might indicate:

- an underlying problem particularly if there have been recurring episodes of a similar nature
  - Consider whether more training may be required on trial procedures at a particular site
  - Repeated non-compliances may accumulate into a potential serious breach
  - A protocol amendment may be appropriate to address a frequently recurring non-compliance issue
- Sites should periodically be sent a copy of the Non-Compliance Log (CCTU/FRM042) displaying their accrued non-compliances (reportable and non-reportable)
- All reportable non-compliances should be evaluated and taken into account for the final Study report

7.2.3. Additional procedure if the episode is categorised as a Potential Serious Breach

All potential serious breaches must be reported to the CCTU Regulatory Team without delay for escalation to the Sponsor: Strict guidelines and time limits apply - follow the procedures outlined by the sponsor in R&D/SOP003 Serious Breach of Protocol or GCP in CTIMPS

8. Monitoring Compliance with and the Effectiveness of this Document

a. Process for Monitoring Compliance and Effectiveness

As part of routine monitoring visits, audit and inspection

b. Standards/Key Performance Indicators

This process forms part of a quality management system and is reviewed according to CCTU procedures. Standard Operating Procedures are reviewed every two years.

9. References

The Institute of Clinical Research, Abbreviations used in Clinical Trials.

MHRA, Good Clinical Practice "Grey Guide"

10. Associated Documents

R&D/SOP003 Serious Breach of Protocol or GCP in CTIMPs

11. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

12. Disclaimer

It is the user's responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

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