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 to identify and handle cases of non-compliance with the trial protocol, standard operating procedures or regulatory requirements to ensure:

- The protection of trial participants
- The maintenance of trial integrity
- 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 the discovery of a course of action or event, which may constitute a:
  - Non-reportable minor non-compliance (Type 1),
  - Reportable Major non-compliance (Type 2) or
  - 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	Waivers are sometimes known as protocol exemptions or authorisations Prospective deviations or waivers to the protocol, are not acceptable as they constitute a deliberate breach of Regulation 29 of SI 2004/1031.

Non-Reportable Minor 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/delayed routine SOC sample collection - Data collection minimally outside of visit window - Participant-derived non-compliances (e.g. refusal/forgetting to take medication, failure to attend a scheduled visit) - Failure of participant to complete a patient reported outcome questionnaire, providing the data is not a primary end point (single episodes)
Reportable Major Non-Compliance (Type 2)	Departure from the protocol, SOP or regulatory requirements that has been identified retrospectively and, is not likely to affect 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/systematic instances of non-reportable non-compliances (Type 1)
Reportable 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 Evidence of systematic Type 2 non-compliances across the trial or across an individual site

3.2. Abbreviations

Abbreviation	**Meaning**
CAPA	Corrective and Preventative Actions
CCTU	Cambridge Clinical Trials Unit
CI	Chief Investigator
CTC	Clinical Trial Coordinator
ISF	Investigator Site File
MHRA	Medicine and Healthcare Products Regulatory Agency
NC (F)	Non-Compliance (Form)
PI	Principal Investigator
QA	Quality Assurance
SOC	Standard of Care
SOP	Standard Operating Procedure
TMF	Trial Master File

4. Undertaken by

The CI and/or PI and their delegates who have a responsibility to comply with this SOP. The CCTU Regulatory Team is responsible for the Sponsor review and categorisation of Type 2 & 3 Non-compliance reports.

5. Items Required

- CCTU/FRM013 Non-Compliance Report Form (includes Impact Assessment)
- CCTU/FRM042 Non-Compliance Log
- CCTU/SOP019 Urgent Safety Measures

6. Summary of Significant Changes

The sponsor representative impact assessment form:

- Will be retained by the regulatory team only
- Will not be sent to the coordination team or participating sites

7. Method

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

7.1. Restrictions

- There are no exemptions to compliance with eligibility criteria listed in the current approved protocol
- All eligibility criteria non compliances are reportable (Type 2 & 3)
- All non-compliances (Type 1, 2 & 3) must be recorded on the non-compliance log CCTU/FRM042

7.2. Once a Non-Compliance is suspected/discovered

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

7.2.1. Non-reportable minor non-compliances (Type 1)

Where an episode is considered a minor non-reportable event, it should be entered into both the site and central Non-Compliance Log (CCTU/FRM042)

Where a non-compliance is discovered centrally by the coordination/ data management team the site team concerned must be informed in order to prevent future occurrences and for inclusion on the local non-compliance log

7.2.2. Reportable major non-compliances (Type 2) and potential serious breaches (Type 3)

Where an event is deemed reportable, populate a Non-Compliance Report Form (CCTU/FRM013) and the Protocol Non-Compliance Log (CCTU/FRM042).

- Where necessary and appropriate members of CCTU can complete the NCF otherwise a member of the site 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 site PI in a timely manner
- The Non-Compliance form should be sent to the CCTU Regulatory Team for review and categorisation in a timely manner following site awareness of the event, usually within 3-5 working days
    - The NCF can be sent to the CCTU Regulatory Team prior to PI & CI signature if this is likely to cause a delay in reporting
- The CCTU Regulatory Team are responsible for reviewing the non-compliance on behalf of the Sponsor to:
    - Determine the categorisation of the non-compliance (Type 1, 2 or 3)
    - Assess the CAPA for applicability/acceptability
    - Perform an impact assessment of the event
- The impact assessment form is retained by the regulatory team
- Any actions required as a result of the impact assessment are communicated by e-mail to:
    - The relevant parties and will be followed up by the regulatory team
    - The CCTU QA Manager for inclusion in the CCTU Learning Log
- If urgent safety measures are required they must be carried out as soon as possible and fully documented, refer to CCTU/SOP019
- The NCF signed by PI (where applicable), CI and the CCTU Regulatory Team must be filed in the sponsor file, TMF and ISF as applicable

7.2.3 Ongoing review of non-compliances

The Non-Compliance Log will be periodically reviewed by the monitor (where a monitor has been assigned) to confirm the categorisation, and by the trial management teams to look for patterns / trends which may indicate an underlying problem particularly recurring episodes of a similar nature.

- A CAPA may be necessary where trends are identified to consider whether:
    - More training is required on trial procedures at a particular site
    - A protocol amendment may be appropriate to address a frequently recurring non-compliance issue
    - Documents may need to be redesigned if they are commonly misunderstood, misread or wrongly completed

- Repeated/systematic major non-compliances can accumulate into a potential serious breach (Type 3)
- The site and central Non-Compliance Log (CCTU/FRM042) displaying all accrued non-compliances (reportable and non-reportable) should be reviewed periodically for reconciliation and central oversight purposes
- All reportable non-compliances should be evaluated and taken into account for the final study report and subsequent publications

7.2.3. Type 3 Non-Compliance - Potential Serious Breaches

- All Type 3 non-compliances/potential serious breaches must be reported to the CCTU Regulatory Team immediately for escalation to the Sponsor
- All non-compliances subsequently categorised as Type 3 by the CCTU Regulatory Team will be escalated to the Sponsor in accordance with 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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