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 classification 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

- Change to reporting responsibilities and timelines section 7.2
- Addition of reporting flow chart section 7.2.3
- Addition of section 7.2.4 Downgraded Classifications
- Addition of Central NC logs being shared with the statistician section 7.2.5

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 site non-compliance log CCTU/FRM042
- All Type 2 and 3 compliances must be recorded on the central 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
- Using the trial specific non-compliance categorisation table in the trial protocol, monitoring plan or trial procedures manual the non-compliance will be classified as is reportable or non-reportable (see 3.1 Definitions)
- Data Managers should be familiar with the trial specific non-compliance categorisation table to help identify NCs at an early stage (e.g. multiple missed visits) and report to the CTC/discuss at the TMG

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 the site 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.

Type 1 non-compliances will be reviewed by the CTC as part of remote monitoring activities.

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

7.2.2.1. Central Team responsibilities

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

- 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)
    - CTC to inform the TMG (including the CI) and if applicable, the involved site PI of the non-compliance
- The Non-Compliance form should be sent to the CCTU Regulatory Team (cuh.cctumonitors@nhs.net) for review and classification in a timely manner following site awareness of the event, within 3 working days
- The NCF signed by the CCTU Regulatory Team must be filed in the TMF and ISF as applicable
- If urgent safety measures are required they must be carried out as soon as possible and fully documented, refer to CCTU/SOP019

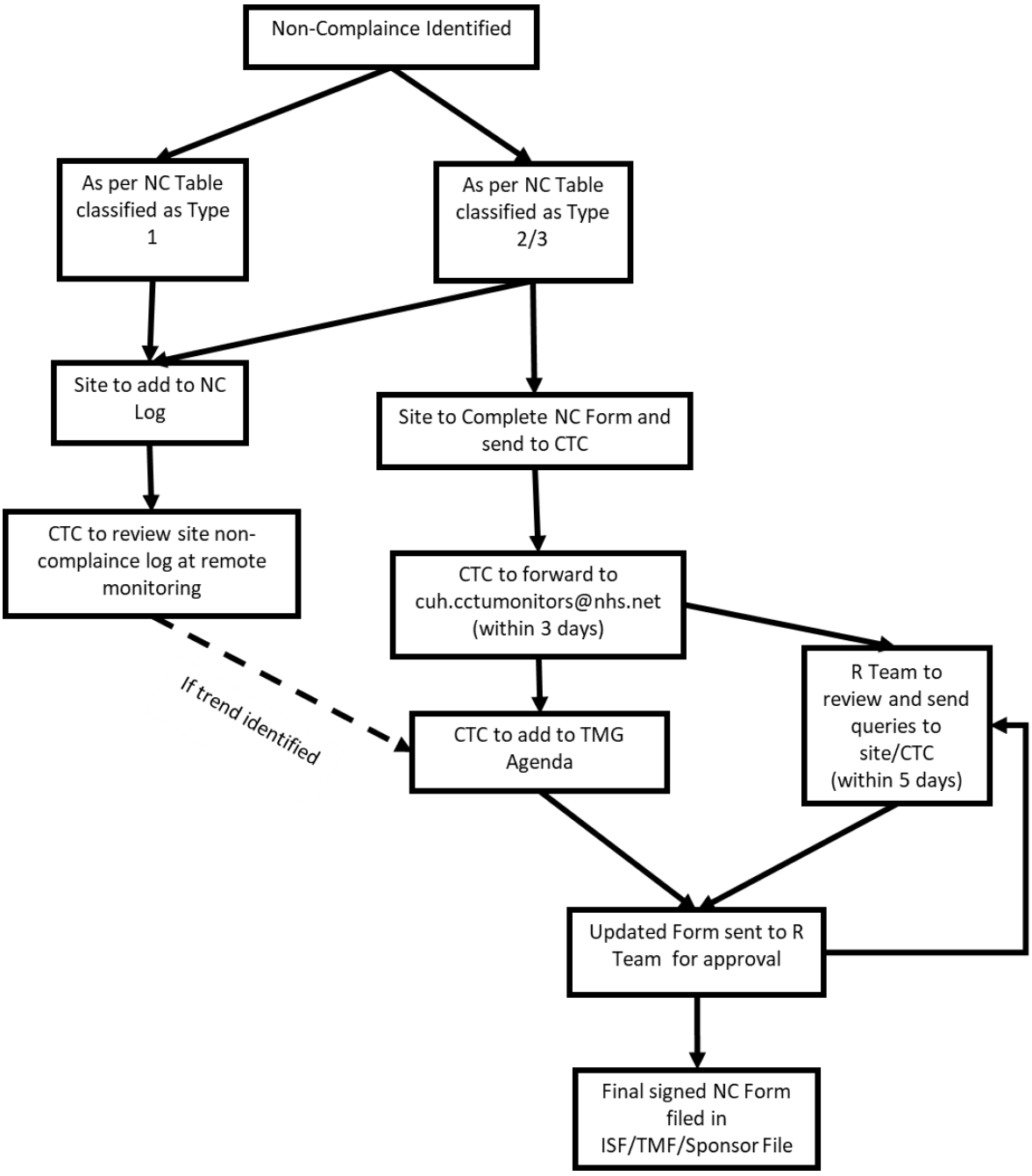
7.2.2.2. Regulatory Team Responsibilities

The CCTU Regulatory Team (predominately the monitor) are responsible for reviewing the non-compliance on behalf of the Sponsor, within 5 working days to:

- Determine the classification 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
- The NCF signed by the CCTU Regulatory Team must be filed in the sponsor file

7.2.3. Flow chart of Reporting



7.2.4. Downgraded Classifications

- If after regulatory review a reportable event is downgraded to a type 1, the non-compliance log is to be updated as applicable. The confirmation of downgrade is to be filed in the in the sponsor file, TMF and ISF as applicable
- If the event is deemed to not be a non-compliance, the entry is to be crossed out on the non-compliance log and any correspondence filed in the sponsor file, TMF and ISF as applicable.

7.2.5. Ongoing review of non-compliances

- The Non-Compliance Log is to be periodically reviewed by the CTC and monitor (where a monitor has been assigned) to confirm the categorisation, classification, and to look for patterns/trends which may indicate an underlying problem, particularly for 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 should be reviewed periodically by the CTC for reconciliation and central oversight purposes
- The Site specific and Central Non-Compliance Logs are to be signed by the respective PI and CI at final close out monitoring visits
- All reportable non-compliances should be evaluated and taken into account for the final study report and subsequent publications. The central NC log is to be shared with the trial statistician alongside any data exports.

7.2.6. 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 classified 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.

Review date	2 years (or earlier in light of new evidence) from approval date
Owning department:	CCTU QA
Supersedes:	CCTU/SOP018 version 8
Local reference:	CCTU/SOP018 version 9