Standard Operating Procedure CCTU/SOP040

Risk Assessment Process for CTIMPS

1. Scope

For use by CCTU staff working on Cambridge Sponsored Clinical Trials of Investigational Medicinal Products (CTIMPs).

The Risk Assessment is completed by the Regulatory team in collaboration with research staff involved in the trial.

This SOP is specifically for CTIMPs, however in the absence of a documented procedure, this can be used as guidance for any other clinical study or trial on the CCTU portfolio.

2. Purpose

This SOP documents the procedure for assessing the risks of a CTIMP during trial set-up. Adequate provisions to mitigate any risk and to monitor the conduct of the trial are based on the risk rating.

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 Sponsored by: Cambridge University Hospitals NHS Foundation Trust (CUH) or CUH jointly with the University of Cambridge or Cambridgeshire & Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge
Sponsor	An individual, company, institution or organisation that takes responsibility for the initiation, management and/or financing a clinical trial
MHRA Type A	Low risk comparable to standard care Low intensity monitoring
MHRA Type B	Higher risk than standard care. Moderate intensity monitoring
MHRA Type C	Markedly higher risk than standard care. High intensity monitoring
Regulatory Team	Regulatory and Quality Manager, Clinical Trials Officers, Clinical Trials Monitors and the Pharmacovigilance Coordinator
Trial Team	Coordinating team and clinical team responsible for running the trial at the sponsor site
Hazard	Anything that may cause harm; also referred to as "risk

	category" in this SOP

3.2. Abbreviations

Abbreviation	Meaning
CTO	Clinical Trials Officer
CCTU	Cambridge Clinical Trials Unit
RQM	Regulatory and Quality Manager
CI	Chief Investigator
PI	Principal Investigator
EU	European Union
CTIMP	Clinical Trial of Investigational Medicinal Product
CTM	Clinical Trials Monitor
CTA	Clinical Trial Application

4. Undertaken by

The CCTU regulatory team trained to this standard operating procedure

5. Items Required

CCTU/FRM021 CTIMP Risk Assessment Form
CCTU/INF009 CCTU Risk Assessment Tool
CCTU/FRM083 CCTU Collaboration Proforma
CCTU/SOP047 Start-up Procedures for Trial Teams
CCTU/SOP048 Start-up Procedures for Regulatory Team
CCTU/FRM011 Monitoring Report Form
R&D/ POL003 Trust Sponsored International Studies

6. Summary of Significant Changes

Change in the trigger for updating risk assessments in process flow

7. Method

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

7.1. Considerations

- Risk to the participants rights
- Risk to the participants integrity, safety and well being
- Risk to the data quality and accuracy of results
- Risk to organisation, resources and staff
- Risk should be determined prospectively and where necessary suitable mitigations should be written into the trial protocol and/ or trial procedures

7.2. Risk Assessment

- The Risk Assessment Process has 2 distinct phases:
- Overall Trial Risk Assessment and Monitoring Risk Assessment
- on-going Risk Assessment

The risk assessment will:

- Identify all hazards
- Based on the hazards, evaluate the likelihood of incidents occurring
- Evaluate severity of such incidents
- Highlight significant and serious risks to patient safety and data integrity
- Aim to mitigate risk
- Assign an overall risk rating of the CTIMP (low, medium and high risk) using the Risk Assessment Tool CCTU/INF009

The risk considerations are documented using CCTU/FRM021 CTIMP Risk Assessment Form. In addition to the above, a MHRA risk rating is also assigned

MHRA Risk Rating

MHRA Trial categories	**Examples**
Type A No higher than that of standard medical care	Trials involving IMPs authorised by any EU member state if: -They relate to the authorised range of indications, dosage or form, or; -They involve off label use, if this off label use is established clinical practice and is supported by sufficient published evidence and/ or guidelines
Type B Somewhat higher than that of standard medical care	Trials involving IMPs authorised by any EU member state if: -Such products are used for a new indication or; -Substantial dose modifications are made for the licensed indication, or; They are used in combination for which interactions are suspected Trials involving IMP not licensed in any EU member state if the drug substance is part of a medicinal product authorised in the EU
Type C Markedly higher than that of standard medical care	Trials involving IMPs not authorised in any EU member state

7.3. Completing the Risk Assessment: General Guidance

The Risk Assessment form is used to document the risk/hazards associated with running a trial and suggests mitigating strategies to minimise the hazard/risk and the parties responsible for implementing the mitigating actions.

Each risk category will have a variety of trial specific risks associated with it; these are recorded in the trial specific Considerations/Concerns Identified column

7.4. Overall Trial Risk Assessment

Considerations of the risk assessment:

- Trial Phase
- IMP
- Intervention, clinical, non-clinical and QA considerations
- Outcome assessments (scans, samplings, biopsies etc.)
- CI/PI experience and reputation
- Resources/ Staffing/ Facilities – both trial team level and CCTU
- Recruitment potential (70 day timeline for first patient recruited – Time & Target, or funder requirements)
- Trial design
- Number of competing studies and patient population
- Participating sites (UK, EU and rest of the world)
- Additional Sponsors

- Note: Should participating sites outside the UK be proposed by the CI of a Trust sponsored CTIMP, inform the Sponsor immediately and refer to R&D POL003 Trust Sponsored International Studies.
- The expertise of specific disciplines must be sought when considering risks that specifically pertain to certain departments or processes:
  - CI/PI
  - CCTU staff – CTO, Statistician, Data Manager and Monitors
  - Affiliated staff – pharmacy, radiology, labs,
  - Sponsor's legal teams
- Use CCTU/FRM021 CTIMP Risk Assessment Form to document the assessment.

7.5. Completing the Risk Assessment

Initiation of the risk assessment is led by a member of the Regulatory team.

Note: When this SOP is followed as guidance for non-CTIMPs, the lead should ideally be the most senior coordinator in the specific CCTU theme; e.g. Cancer Coordination Team Lead for non-CTIMPs falling under the Cancer Theme.

- The risk assessment process will begin once funding has been confirmed, but must be finalised prior to any trial initiation activities being undertaken
- Use form CCTU/FRM021 to determine whether the trial is considered to be Type A or B/C in relation to the MHRA trial categories
- The form is also used to record:
  - Risks/hazards associated with the trial
  - Specific considerations
  - Risk ratings
  - Mitigating strategies
  - Risk rating after mitigation

  - Actions required to mitigate the risk and responsible parties
- Use the CCTU Risk Assessment Tool CCTU/INF009 to rate the likelihood and the consequences of the risk, to obtain the risk rating which also forms the basis of the monitoring plan
- The final risk rating is recorded at the end of the risk assessment form along with any trial specific issues that should be included in the monitoring plan
- Once finalised the document must be reviewed and approved by the CCTU Operations Director or delegate, the CI Pharmacy and others as necessary
- A signed copy should be filed in the sponsor file, and a copy provided to the Sponsor, and trial team by email
- For a non-CTIMP it will be held by the CCTU
- All mitigating actions identified for completion by the trial team, and the deadline for each actions completion will be communicated by email to the trial team normally within 5 working days of the final document approval
- The Regulatory Team are responsible for ensuring that all mitigating actions are completed by the required deadlines

It may be necessary to update the risk assessment form prior to trial initiation or at any point during the trial if for any reason there is a change in:

- The trial design
- Responsibilities and procedures
- The conduct of the trial, including significant changes to sites or patient numbers
- The quality of the conduct of the trial

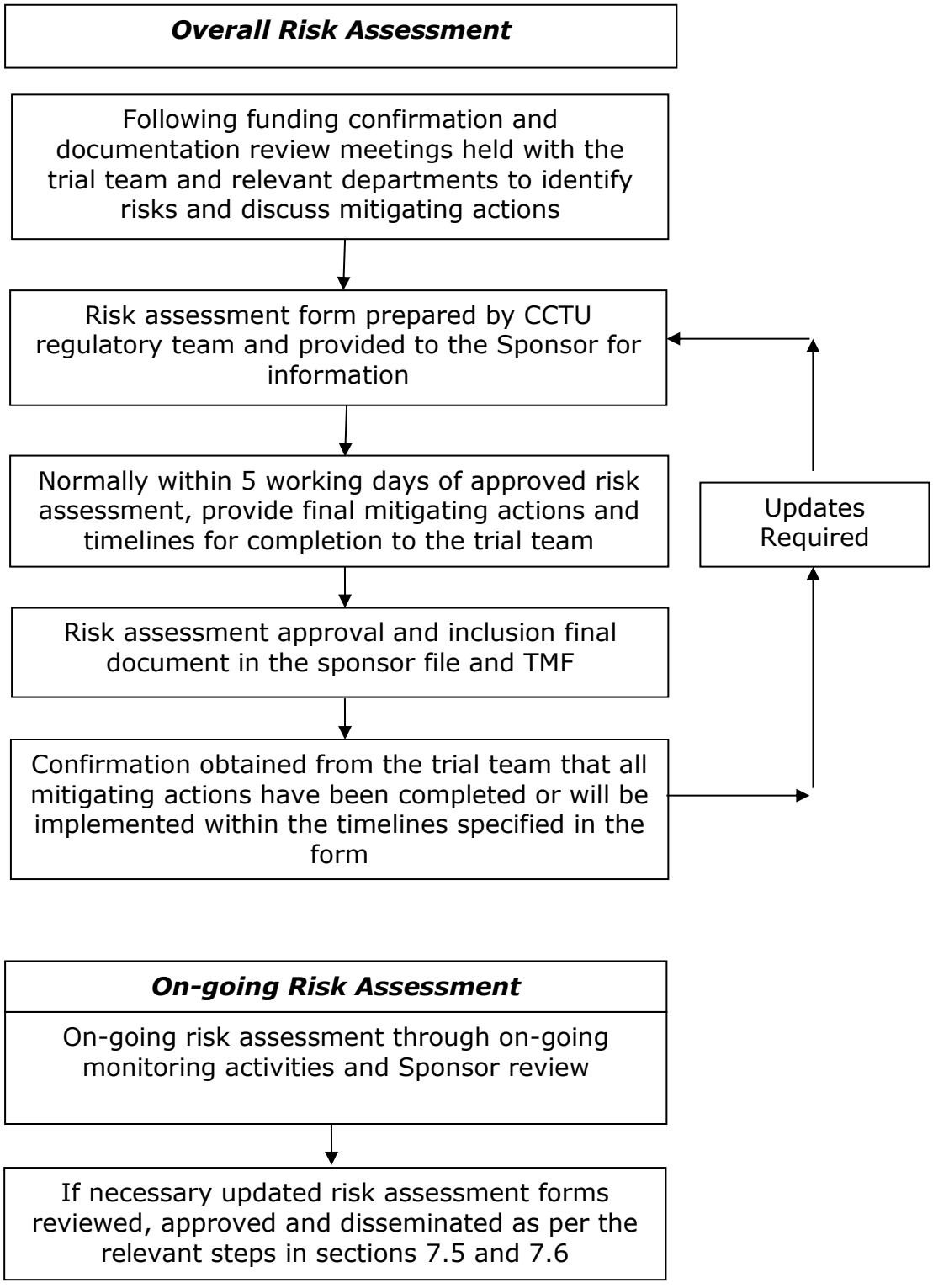
As necessary, the changes will be made to CCTU/FRM021 and version controlled as appropriate. The same process and timelines for review, approval and dissemination of information must be followed as above.

7.6. On-going Risk Assessment - Change to the Risk or Requirements for Additional Mitigating Actions

- During the lifetime of the trial the risk rating may change
- On-going risk assessment and documentation review will be completed during monitoring visits and other sponsor review processes
- The risk assessment form will be updated at any stage of the trial if it is deemed appropriate
- Changes to the risk rating that affect the management, conduct or monitoring frequency of the trial will:
  - Be recorded in an updated risk assessment form the reason and summary of change will be recorded in the review and revision section
  - Be used to update the monitoring plan if appropriate
  - Be communicated to the Sponsor and trial team in monitoring feedback letters or as set out in section 7.5
- All additional mitigating actions identified must be implemented by the responsible parties within the timelines specified and communicated

- The regulatory team must obtain confirmation from the responsible parties that all mitigating actions have been completed/implemented and this confirmation provided to the Sponsor to inform their continued sponsorship decision processes
- Note: For all trials where the risk assessment was documented as part of the previous 2 part assessment process, the risks and monitoring frequency will be updated on the existing forms for that trial.

7.7. Process Flow



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

CCTU/SOP007 CCTU Escalation Cascade

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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