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**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Cambridge Sponsored</td>
<td>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 &amp; Peterborough NHS Foundation Trust (CPFT) or CPFT jointly with the University of Cambridge</td>
</tr>
<tr>
<td>Sponsor</td>
<td>An individual, company, institution or organisation that takes responsibility for the initiation, management and/or financing a clinical trial</td>
</tr>
<tr>
<td>MHRA Type A</td>
<td>Low risk comparable to standard care Low intensity monitoring</td>
</tr>
<tr>
<td>MHRA Type B</td>
<td>Higher risk than standard care. Moderate intensity monitoring</td>
</tr>
<tr>
<td>MHRA Type C</td>
<td>Markedly higher risk than standard care. High intensity monitoring</td>
</tr>
<tr>
<td>Regulatory Team</td>
<td>Regulatory and Quality Manager, Clinical Trials Officers, Clinical Trials Monitors and the Pharmacovigilance Coordinator</td>
</tr>
<tr>
<td>Trial Team</td>
<td>Coordinating team and clinical team responsible for running the trial at the sponsor site</td>
</tr>
<tr>
<td>Hazard</td>
<td>Anything that may cause harm; also referred to as “risk”</td>
</tr>
</tbody>
</table>
3.2. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTO</td>
<td>Clinical Trials Officer</td>
</tr>
<tr>
<td>CCTU</td>
<td>Cambridge Clinical Trials Unit</td>
</tr>
<tr>
<td>RQM</td>
<td>Regulatory and Quality Manager</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>CTIMP</td>
<td>Clinical Trial of Investigational Medicinal Product</td>
</tr>
<tr>
<td>CTM</td>
<td>Clinical Trials Monitor</td>
</tr>
<tr>
<td>CTA</td>
<td>Clinical Trial Application</td>
</tr>
</tbody>
</table>

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**

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

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

**Overall Risk Assessment**

- Following funding confirmation and documentation review meetings held with the trial team and relevant departments to identify risks and discuss mitigating actions

- Risk assessment form prepared by CCTU regulatory team and provided to the Sponsor for information

- Normally within 5 working days of approved risk assessment, provide final mitigating actions and timelines for completion to the trial team

- Risk assessment approval and inclusion final document in the sponsor file and TMF

- Confirmation obtained from the trial team that all mitigating actions have been completed or will be implemented within the timelines specified in the form

**On-going Risk Assessment**

- On-going risk assessment through on-going monitoring activities and Sponsor review

- If necessary updated risk assessment forms reviewed, approved and disseminated as per the relevant steps in sections 7.5 and 7.6
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.

<table>
<thead>
<tr>
<th>Review date</th>
<th>2 years (or earlier in light of new evidence) from approval date</th>
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</thead>
<tbody>
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<td>Owning department:</td>
<td>CCTU QA</td>
</tr>
<tr>
<td>Supersedes:</td>
<td>CCTU/SOP040 V4</td>
</tr>
<tr>
<td>Local reference:</td>
<td>CCTU/SOP040 V5</td>
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