University of Hertfordshire

RISK ASSESSMENT PROCESS

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for Risk Assessment and Risk Rating for Research Studies at the University of Hertfordshire

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Version Number: 2	**Review Date:** 3 years (or as required)

1.0. BACKGROUND

This is a University of Hertfordshire (UH) Standard Operating Procedure (SOP). SOPs are required to assist researchers in conducting research in accordance with the principles of Good Clinical Practice (GCP) and relevant regulations and guidance.

Sponsors have a duty to provide oversight of research studies to ensure there is adequate protection of participant's safety and rights and data integrity. However, there are inherent risks. The purpose of a risk assessment is to:

- Identify all hazards
- Evaluate the likelihood of incidents occurring, based on the identified hazards, and their severity
- Highlight significant and serious risks to patient safety and data integrity
- Establish "tolerance" limits
- Aim to mitigate risk
- Assign an overall risk rating of the CTIMP (low, medium and high risk)
- Assign an MHRA risk rating

The Risk Assessment process has three distinct phases:

1. High level/pre-funding risk assessment
2. Post funding study detailed risk assessment
3. On-going risk assessment

For CTIMPs, the high level risk assessment advises whether the study is considered to be Type A or Type B/C in relation to the MHRA Trial Categories (Appendix 1) and informs the CTSNMG/AGRCGS and CTSN whether the study is to be put through a full Clinical Trial Authorisation (CTA) application or the notification scheme.

For all studies, the relevant risk assessment will advise whether the study is considered very high, high, medium, or low risk.

2.0. PURPOSE

The purpose of this document is to describe the procedures to be followed by all research staff who are involved in assessing the risks of Clinical Trials of Investigational Medicinal Products (CTIMPs) and Non-CTIMPs throughout the study.

This SOP documents the procedures to produce a risk assessment document for clinical studies sponsored/co-sponsored by UH and/or adopted by the CTSN. Adequate provision to mitigate the risk and to monitor the conduct of the trial should then be made, based on the risk rating.

3.0. APPLICABLE TO

This SOP is applicable to all research staff working on clinical studies sponsored/co-sponsored by UH and/or adopted by the CTSN.

4.0. RESPONSIBILITIES

4.1. The Sponsor:

- should be aware of the potential foreseeable risks and hazards associated with a specific study and the 'harm' that hazard would result in, should it occur, prior to agreeing to act as sponsor
- is responsible for the evaluation of risks of a study, although they may delegate some of the tasks to a competent member of the CTSN

4.2. If adopted by the CTSN, the CTSN:

- will facilitate the completion of Part 1 of the risk assessment form (UH CTSN TP-30)
- will work closely with the Chief Investigator and the study team to complete Part 2 of the risk assessment form (UH CTSN TP-30) to identify study risks and agree mitigating and monitoring actions
- support the CI in reviewing and updating the risk assessment

4.3. The Chief Investigator:

- and their study team will complete the risk assessment and where necessary involve other staff with expertise in difference fields e.g., Pharmacist, Statistician, Clinical Trial Manager, Data Managers and Research Nurses
- will have primary responsibility for ensuring any actions arising from the risk assessment are carried out as necessary (this will be supported, where applicable, by the CTSN)
- will manage the risk assessment, including reviewing and updating as necessary

5.0. PROCEDURE

5.1. General Guidance

Considerations of the Risk Assessment process are as follows:

- Trial Phase
- Investigational Medicinal Product (IMP)
- Intervention, clinical, non-clinical and quality assurance considerations

- Outcome assessments (scans, samplings, biopsies etc.)
- CI/PI experience and reputation
- Resources/Staffing/Facilities
- Potential/confirmed funding
- Recruitment potential
- Study design
- Number of competing studies and patient population
- Participating sites (UK, EU and rest of the world) – should participating sites outside the UK be proposed by the CI of a Trust sponsored CTIMP, inform the Sponsor immediately.

The expertise of the following specific disciplines must be sought when considering risks that specifically pertain to certain departments or processes:

- CI/PI
- Clinical Trials Support Network Staff (CTSN) – Clinical Trial Monitor, Statistician etc.
- Sponsor's legal advice (if required)

There is also the option within the Risk Assessment to record specific instructions for trial management that are required to mitigate risk or to record activities that are not required (e.g., accountability on low-risk standard of care CTIMPs).

For CTSN adopted studies the Risk Assessment informs the creation of the Quality Management and Monitoring Plan (QMMP)/Monitoring Plan and Safety Monitoring Plan (SMP) and the decisions surrounding the frequency and type of monitoring to be carried within the study.

5.2. Acceptable Limits of Risk

5.2.1. For studies sponsored by UH and/or adopted by the CTSN

High Risk

- If any section is rated high or very high risk, after mitigating factors have been taken into account, the study will not be accepted for sponsorship.
- Sponsorship will be reconsidered only once it has been demonstrated by the CI that appropriate mitigating factors have been implemented to reduce the likelihood of risk to at least medium risk level.

Medium Risk

- If any section is rated medium risk, after mitigating factors have been taken into account this will trigger a monitoring plan reflective of the level of risk.
- The monitoring plan will be reviewed and updated if the level of risk is reduced by subsequent mitigating factors.

Low Risk

- If the overall outcome of the risk assessment is low, the monitoring plan will be reflective of this level of risk.
- The monitoring plan will be reviewed and updated if the level of risk alters during the study (see gSOP-12 Monitoring).

- Assessed risks must be within these acceptable limits of risk as defined above to be accepted for UH sponsorship and/or adopted by the CTSN.
- If risks are identified which are not appropriately managed/mitigated by the CI and study team, the CI or Trial Manager will liaise with the CTSN. The CTSN will decide appropriate action. If risks are not satisfactorily managed/mitigated this may affect study set-up activity and the study could be put on hold.

5.2.2. For studies not adopted by the CTSN

- Planned research not sponsored by UH or adopted by the CTSN but carried out by staff at UH should be evaluated for risk using the UH Risk Assessment Form found on HertsHub, or adapted school specific Risk Assessment Form. School specific Risk Assessment Forms can be obtained by contacting the relevant safety contact. Acceptable limits of risk in this case are as follows:

Risk Level		Suggested Action(s) to Manage Risk
Low	**1-4**	No further risk controls should be required. Continue to monitor the work/activity. Observe that existing controls are being maintained/followed. Review if there are any changes in the level of risk e.g., following an incident or from a change of equipment/process.
Medium	**5-9**	Aim to reduce the risk where reasonably practicable (balancing the need to reduce the risk with the level of cost, time and effort required to achieve this). Continue to monitor the work/activity. Observe that existing controls are being maintained/followed. Review if there are any changes in the level of risk e.g., following an incident or from a change of equipment/process.
High	**10-16**	You must consider ways to reduce the risk further and/or change the work/activity so it can be done in a safer way. If the risk remains high, you will need to consider using the best available resources to achieve this. Continue to monitor the work/activity. Observe that existing controls are being maintained/followed. Review if there are any changes in the level of risk e.g., following an incident or from a change of equipment/process.
Very High	**20-25**	The work/activity must not start or continue until the risk has been reduced e.g., changing the work/activity so it can be done in a safer way. If it is not possible to reduce the risk, even with the best available resources, the work/activity must be prohibited.

5.3. Completing the Risk Assessment

Items required to complete the Risk Assessment:

- Risk Assessment Flow Chart (Appendix 2)
- Relevant Risk Assessment Form (UH CTSN TP-30 for studies adopted by the CTSN)
- Risk Assessment Guidance (UH CTSN GU-08 if using UH CTSN TP-30)

- Documented delegation of responsibility for co-sponsored studies (if applicable)

When completing the risk assessment for a CTIMP, consideration of the reference safety information that will be used should include how often this information should be updated.

5.3.1. Pre-Funding Risk Assessment

5.3.1.1. Risk Assessment Form Part 1

- Part 1 of the Risk Assessment Form should be completed if the study has not yet received funding. If the study has successfully obtained funding, please go to section 5.2.2 of this SOP.
- Send the completed Part 1 Risk Assessment form to the CTSN (uhclinicaltrialsupportnetwork@herts.ac.uk) for review.
- For studies requesting UH Sponsorship/co-sponsorship, once reviewed by the CTSN, the Part 1 Risk Assessment form should be sent to Research Sponsorship (research-sponsorship@herts.ac.uk), for review and approval.
- The approved copy should be filed in the Sponsor file.

5.3.2. Post-funding Risk Assessment

5.3.2.1. Studies Not Adopted by the CTSN

- A full risk assessment should be conducted post funding for all studies.
- Planned research not sponsored by UH or adopted by the CTSN but carried out by staff at UH should be evaluated for risk using the UH Risk Assessment Form found on HertsHub. or adapted school specific Risk Assessment Form. School specific Risk Assessment Forms can be obtained by contacting the relevant safety contact.
- Risks should be monitored throughout the study and should any amendments occur, these should be reflected within the appropriate Risk Assessment Form.

5.3.2.2. Studies Adopted by the CTSN

- For studies adopted by the CTSN, parts 2, 3, and 4 of the Risk Assessment form (TP-30) should be completed. See below and guidance (UH CTSN GU-08) for further details.

5.3.2.2.1. Completion of Risk Assessment Form Part 2

- Once the study has successfully obtained funding, Part 2 of the Risk Assessment form should be completed. Part 2 of the assessment should have input from all stakeholders involved in the study:
    - CI/PI
    - CTSN staff, Statistician, Clinical Trial Pharmacists
    - for co-sponsored studies, a representative from the co-sponsor

- The above parties should be sent a final draft protocol prior to submission to any regulatory review body, so that feedback/risk mitigation measures can be incorporated into the protocol prior to finalisation for submission.
- CTIMP studies involving healthy volunteers will be highlighted during the feasibility and sponsor review of the study. If it is deemed appropriate to implement The Over-Volunteering Prevention System (TOPS) this must be documented in the feasibility and sponsor risk assessment.
- The Risk Assessment Part 2 is completed by the CTSN, seeking input from the wider study team, with reference to completed Risk Assessment Part 1 (if applicable) and in discussion with the assigned study monitor, where appropriate.

5.3.2.2.2. Completion of Risk Assessment Form Part 3

- Part 3 of the Risk Assessment form includes four tables which should be completed in order produce a risk score based on the impact of the risk and the probability/likelihood of it occurring.
- The risk score should be carefully considered by the wider study team who should help justify the scores both pre and post risk reduction strategy implementation. Assessed risks must be within the acceptable limits of risk as aforementioned situation to be accepted for sponsorship and/or adopted by the CTSN. UH CTSN GU-08 Risk Assessment Guidance provides further guidance for risk rating assessment criteria.
- The tables enable evaluation of the risks associated with:
    - the rights and safety of participants
    - project concept (design) and the reliability of results
    - project management and governance
    - other considerations
- Once all relevant sections of the risk assessment have been finalised, it should be sent to the CTSN (uhclinicaltrialsupportnetwork@herts.ac.uk) for review.
- Once approved by the CTSN, it should be sent to the AGRGCS, via Research Sponsorship (research-sponsorship@herts.ac.uk), for review.

5.3.2.2.3. Completion of Risk Assessment Form Part 4

- If approved by the AGRGCS following review, Part 4 of the Risk Assessment Form will be completed and signed by relevant signatories prior to the study starting.
- Should any amendments affect risk of the study, the Risk Assessment will need to be updated, reviewed, and signed again by the relevant signatories.

5.3.3. Ongoing Risk Assessment

- During the lifetime of the trial the risk rating may change.
- The Risk Assessment should be updated when any changes to the protocol or other aspects of trial conduct impact on safety, data, operational and monitoring activities. Updated risk assessment documentation will be completed at any stage if it is deemed appropriate and reviewed by the CTSNMG/AGRGCS.

- Changes to the risk that affect the monitoring frequency will be recorded in the trial QMMP/Monitoring plan and communicated to the Sponsor and trial team via the monitoring feedback letters.

6.0. REFERENCES AND LINKS TO OTHER DOCUMENTS

- Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products
- The MHRA Good Clinical Practice Guide "Grey Guide" p402, Published 2012
- gSOP-02 – Adverse Event Reporting
- UH CTSN TP-30 Risk Assessment Form
- UH CTSN GU-08 Risk Assessment Guidance
- UH CTSN TP-80 QMMP Template
- gSOP-12 Monitoring
- UH Risk Assessment

7.0. APPENDICES

7.1. Appendix 1 – Definitions
7.2. Appendix 2 – MHRA Trial Categories
7.3. Appendix 2 – Risk Assessment Flow Chart

8.0. AUTHORSHIP & APPROVAL

Author **Megan Smith**

Signature  **Date 25/07/22**

Pro Vice-Chancellor (Research & Enterprise) Approval
Professor J M Senior

Signature  **Date 08/08/2022**

9.0. VERSION HISTORY/REVISIONS

Version Number	Effective Date	Reason for Change

10.0. AGREEMENT

Please detach and retain within <u>your training files</u>

I have read and understood the contents and requirements of this SOP (ref gSOP-030-02) and accept to follow University policies implementing it.

Recipient
Signature: ……Date: ……..
Name & Position: ……

Appendix 1: Definitions

Adverse Event (AE)
Any untoward occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Chief Investigator (CI)
A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Trial
A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or control) to evaluate the effects of those interventions on health outcomes.

Clinical Trial of Investigational Medicinal Product (CTIMP)
A study that looks at the safety or efficacy of a medicine/food stuff/placebo in humans as defined by the Medicines for Human Use Regulations (2004).

Investigational Medicinal Product (IMP)
A pharmaceutical for an active substance or placebo being tested or used as a reference in a clinical trial. This includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial -

- Used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,
- Used for an indication not included in the summary of product characteristics under the authorisation for that product, or
- Used to gain further information about the form of that product as authorised under the authorisation.

Monitoring
A quality control (QC) activity which involves a system of ongoing real time checks to detect discrepancies and faults, in order to correct them, and prevent the failure from recurring so that the specified output is produced consistently, in this context compliance with the UK Regulations, Sponsor SOPs, approved protocol and GCP.

Monitoring Plan
The agreed process for monitoring a CTIMP sponsored by UH as specified in the study monitoring plan determined by the risk based monitoring strategy.

Principal Investigator (PI)
A Registered Physician, Dentist, Pharmacist or Registered Nurse who has responsibility for the conduct of the trial at a host site.

Quality Control (QC)
The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

The Medicines & Healthcare Products Regulatory Agency (MHRA)

UK Competent Authority responsible for regulation of Clinical Trials.

Trial Management Group (TMG)
The Trial Management Group for each trial is set up to oversee the clinical and practical aspects of the day to day management of the trial. The TMG normally includes individuals such as the Chief Investigator, Trial Physician(s), Statistician, Trial Coordinator, Research Nurse, and Data Manager(s). The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

Trial Master File (TMF)
The Trial Master File (TMF) will be held at the principal site by the Sponsor, Chief Investigator or at the coordinating centre. The TMF should contain all essential documents defined as documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced. A TMF should be set up at the beginning of a trial and maintained up to date throughout the trial until trial conclusion.

For trials currently running, it is recommended that Section 8 of the ICH-GCP Guideline is followed as guidance in order to meet statutory requirements. However, some of the documents listed may not be available or applicable in many non-commercial trials. The appropriate documentation will vary according to the trial and Sponsor Requirements.

Type A Clinical Trial
A clinical trial but with no higher risk than standard medical care. The medicinal product must be licensed in an EU Member State and the trial relates to the licensed range of indications, dosage and form or, the trial involves off-label use (such as in paediatrics and in oncology), if this off- label use is established practice and supported by sufficient published evidence and/or guidelines.

Type B Clinical Trial
A clinical trial but with somewhat higher risk than standard medical care and involving medicinal products licensed in any EU Member State if such products are used for a new indication (different patient population/disease group), or substantial dosage modifications are made for the licensed indication or if they are used in combinations for which interactions are suspected. Also, trials involving medicinal products not licensed in any EU Member State if the active substance is part of a medicinal product licensed in the EU.

Type C Clinical Trial
A clinical trial but with markedly higher risk than standard medical care and involving a medicinal product not licensed in any EU Member State. A grading other than type C may be justified if there is extensive class data or pre-clinical and clinical evidence.

Appendix 2: MHRA Trial Categories

MHRA Trial categories	
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.

Appendix 2: Risk Assessment Decision Flow Chart