

University of Hertfordshire

RISK ASSESSMENT AND RISK RATING FOR CTIMPs

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for Risk Assessment and Risk Rating for Clinical Trials of Investigational Medicinal Products (CTIMPs) at the University of Hertfordshire

SOP Number: gSOP-33-02	Effective Date: 16 th March 2022
Version Number: 2.0	Review Date: 3 years (or as required)

1.0 BACKGROUND

This is a University of Hertfordshire standard operating procedure. University of Hertfordshire (UH) acknowledges West Hertfordshire Hospitals NHS Trust (WHHT) Research & Development (R&D) which has allowed UH to use the SOPs developed by WHHT where possible, modified for local implementation.

2.0 PURPOSE

To document the procedures to be followed by all research staff who are involved in the assessment of the risk and to produce a risk assessment document for clinical trials sponsored/co-sponsored or managed by the University of Hertfordshire. Adequate provision to mitigate the risk and to monitor the conduct of the study should then be made.

3.0 APPLICABLE TO

For use by research staff working on Clinical Trials of Investigational Medicinal Products (CTIMPs). This SOP is specifically for CTIMPs, however in the absence of a documented procedure can be used as guidance for any other clinical study.

For co-sponsored studies the Risk Assessment is completed by UH staff working in collaboration with R&D staff.

4.0 RESPONSIBILITIES

This applies to any UH employee involved with research which requires UH sponsorship/co-sponsorship including but not limited to: Chief Investigators, Principal Investigators, Research Fellows, Consultants, Statisticians, Clinical Trial Pharmacists, Research Managers, Research Nurses, Clinical Trial Practitioners, Allied Health Professionals, Trial Managers, Clinical

Studies Officers, Data Managers and Research Assistants.

5.0 PROCEDURE

Items Required:

- Risk assessment Flow Chart (Appendix 2)
- CTIMP Risk Assessment: Part 1
- CTIMP Risk Assessment: Part 2
- Documented delegation of responsibility for co-sponsored studies

The risk assessment must:

- Identify all hazards
- Evaluate the likelihood of incident and 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

MHRA Risk rating

MHRA Trial categories	
Type A No higher than that of standard medical care	Trials involving IMPs authorised by any EU member state if: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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.

For a CTIMP the risk assessment process should be undertaken by a multi-disciplinary team able to consider all the various aspects of the trial. This should include as a minimum: Chief investigator, pharmacist, clinical trial manager. Other personnel such as a statistician, data managers and research nurses may be required depending on the complexity of the study.

The risk considerations will be collated into the CTIMP Risk Assessment Part 1 and CTIMP Risk Assessment Part 2.

The Risk Assessment Process has 3 distinct phases:

- Phase 1 - Initial High Level Risk Assessment (Pre-funding Part 1)
- Phase 2 – Post funding Study Details Risk Assessment (Part 2)
- Phase 3 - Ongoing Risk Assessment

5.1 Completing the Risk Assessment: General Guidance

The Risk Assessment process has been split into two parts:

- Potential studies are referred to the University of Hertfordshire Advisory Group on Research Governance for Clinical Studies (AGRCS)/Clinical Trial Support Network Management Group (CTSNMG) for discussion. Risk assessment Part 1 is completed. The outcome of this assessment informs the Sponsorship in principle decision. For co-sponsored studies all documents to be agreed with the co-sponsor.
- Part 2 is a full identification and mitigation of risks associated with the study.
- The expertise of specific disciplines must be sought when completing both parts of the risk assessment (e.g. Pharmacy for CTIMPs).
- The initial risk assessment information should be used to rate the likelihood and the consequences of the risk.

5.1.1 Phase 1: – High Level (pre-funding) Risk Assessment (Part 1 of Risk Assessment Template)

- Considerations in this first stage of the Risk Assessment Process:
 - o Trial Phase
 - o Investigational Medicinal Product (IMP)
 - o Intervention, clinical, non-clinical and Quality Assurance considerations
 - o Outcome assessments (scans, samplings, biopsies etc.)
 - o CI/PI Experience and reputation
 - o Resources/Staffing/Facilities
 - o Potential/Confirmed Funding
 - o Recruitment Potential (70 day timeline for first patient recruited – Time & Target)
 - o Study design
 - o Number of competing studies and patient population
 - o Participating sites (UK, EU and rest of the world)

Note: Should participating sites outside the UK be proposed by the CI of a Trust sponsored CTIMP, inform the Sponsor immediately.

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

- o CI/PI
- o Clinical Trials Support Network Staff – Clinical Trial Monitor, Statistician
- o Sponsor’s legal advice (if required)

For CTIMPS Part 1 of the Risk Assessment is led by an appropriate member of the CTSN/ADR on behalf of the CTSNMG/Advisory group for research governance of clinical studies (AGRGCS) liaising with the CI.

- The risk assessment advises whether the trial is considered to be Type A or Type B/C in relation to the MHRA Trial Categories.
- The risk rating will also inform the CTSNMG/AGRGCS as to whether the trial is to be put through a full Clinical Trial Authorisation (CTA) application or the notification scheme.
- There is also the option 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).
- When completing the risk assessment consideration of the reference safety information that will be used should include how often this information should be updated.
- Once Part 1 is finalised it should be sent to the AGRGCS, via Research Sponsorship, for review.
- The approved copy should be filed in the Sponsor file.

5.1.2 Phase 2 – Study Details for Post-funding Risk assessment (Part 2 of Risk Assessment Template)

The assessment has input from all stakeholders involved in the study:

- Chief Investigator/Principal Investigator
- CTSN staff, Statistician, Clinical Trial Pharmacists
- for co-sponsored studies, a representative from the co-sponsor

These 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 informs the creation of the Quality Management and Monitoring Plan and the decisions surrounding the frequency and type of monitoring to be carried within the study.

The Risk Assessment Part 2 is completed by the CTSN and CI with reference to completed Risk Assessment Part 1, and where appropriate, in discussion with assigned study monitor. Guidance is available from the CTSN.

- Once part 2 is finalised it should be sent to the AGRGCS, via Research Sponsorship, for review.

5.1.3 Phase 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 Quality Management and Monitoring Plan and communicated to the Sponsor and trial team via the monitoring feedback letters.

6.0 REFERENCES and LINKS TO OTHER SOPS AND 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
- gSOP02 – Adverse Event Reporting
- UH CTSN TP-30 Risk Assessment Form v2.0
- UH CTSN GU-08 Risk Assessment Guidance v1.0
- UH CTSN TP-XX QMMP Template v1.0

7.0 APPENDICES

- 7.1 Appendix 1 - Definitions
- 7.2 Appendix 2 – Risk Assessment Flow Chart

8.0 AUTHORSHIP & APPROVAL

Author Solange Wyatt

Signature  **Date** 15/03/2022

Pro-Vice Chancellor (Research & Enterprise) Approval

Signature  **Date** 01/03/2022

9.0 VERSION HISTORY/REVISIONS

Version Number	Effective Date	Reason for Change
1.0	26.th April 2018	Introduction of updated Risk Assessment Template, Risk Assessment Guidance and QMMP

10.0 AGREEMENT

Please detach and retain within your training files

I have read and understood the contents and requirements of this SOP (ref gSOP-033-02) and accept to follow University policies implementing it.

Recipient

Signature:Date:

Name & Position:

Please retain copy of the signed form for your reference in your training file

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 Trial

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: Risk Assessment Decision Flow Chart

