

University of Hertfordshire

RISK ADAPTED APPROACH TO CTIMPS

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for a Risk Adapted approach to the management of clinical trials of investigational medicinal products sponsored/co-sponsored or managed by the University of Hertfordshire.

SOP Number: gSOP-37-01	Effective Date: 05 June 2018
Version Number: 1.0	Review Date: 3 years (or as required)

1. BACKGROUND

This is a University of Hertfordshire standard operating procedure. Where there are potential conflicts between different collaborating organisations' SOPs, project level working instructions should be developed, to determine precedence.

For every clinical trial of an investigational product (CTIMP) there are a core set of risks inherent to the protocol that relate to the safety of the participant and the integrity/reliability of the results. This SOP details the processes involved to identify these risks so that control measures, resources, procedures and processes can be implemented during the trial to ensure patient safety and lead to high quality results.

The potential risks in regard to patient safety need to be balanced against the level of risk a trial participant would be exposed to outside the trial.

2. PURPOSE

This document details the requirements for pragmatic risk assessment for clinical trials to aid compliance with the regulatory framework and GCP. The regulatory framework in the UK provides for a simple risk categorisation based on the marketing status of the drug and standard medical care. This SOP details a range of risk-adapted approaches that are possible to simplify the process involved in initiating and managing a clinical trial. Further information on this approach can be found in the MRC/DH/MHRA paper "risk adapted approached to the management of clinical trials of investigational medicinal products".

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

3. APPLICABLE TO

This applies to any UH employee involved with research which requires UH sponsorship/co-sponsorship or management 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. For use by all UH research staff working on Clinical Trials of Investigational Medicinal Products (CTIMPs).

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

4. RESPONSIBILITIES

The trial sponsor is responsible for the management of a clinical trial including the evaluation of the risks although they may delegate some of the actual tasks to a competent member of the study team. This delegation should be agreed and documented.

The Chief Investigator or delegated individual (DI) is responsible for overseeing the mitigations or actions planned from the risk assessment. This should be documented in the Trial Master File.

5. PROCEDURE

5.1 Assessment of risks in Clinical Trials

Risk in a Clinical Trial can be defined as the likelihood of a potential hazard occurring and causing harm to the trial participant and / or an organisation, or detrimentally affecting the reliability of the trial results.

Risk assessment is the process of identifying the potential hazards associated with the trial and assessing the likelihood of the hazards occurring and resulting in harm.

The risk assessment must be customised to each individual Clinical Trial (See gSOP-033).

The potential risks should be balanced against the level of risk that a trial participant would be exposed to outside the trial.

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 or DI; NHS Pharmacist; Clinical Project Manager. Other personnel such as a Statistician, Data Managers, and Research Nurses may be required depending on the complexity of the study. Studies involving NHS partner organisations should involve NHS R&D department.

The risk assessment should identify any potential risks in the trial that need to be mitigated by monitoring and management activities. The risk assessment process must be initiated prior to the finalisation of the protocol as the risk assessment and mitigation may influence the trial design and trial procedures.

The nature and extent of possible adaptations should be determined during the trial set up phase, detailed in the Risk Assessment documents and stored in the Trial Management File.

The risk assessment process must document:

- a) Justification as to the chosen risk level (Type A, B or C as shown in Table A below) including reference to current care, evidence of drugs current license / established use and quoting any appropriate established guidelines.
- b) The potential risks to trial participants and to the reliability of trial results and the actions necessary to mitigate them. The risk assessment must include IMP and non IMP risks. Consideration should be given to follow-up of female partners of male subjects depending on the safety profile of the drug (e.g. if it is known to have an effect on spermatogenesis).
- c) The potential risks to the reliability of the results and actions necessary to mitigate against them.
- d) In addition the following aspects should be considered:
 - Which key trial documents are required
 - The input required from the members of the trial team or external experts
 - Trial management requirements, which will identify the planning and resource aspects of the trial (e.g., trial monitoring requirements)
 - Selection of site/s and the type of site assessment that is appropriate for the trial and site (e.g., pre-qualification questionnaire vs on-site visit)
 - The need to sub-contract any study activities
 - Adverse event reporting
 - Type and frequency of monitoring
 - IMP storage and documentation requirement
 - The requirement for a Data Monitoring Committee as part of the oversight and management of the trial

5.2 Possible risk adaptations

- 5.2.1 Once the risk level has been identified the possible adaptations can be considered to the management of the Clinical Trial. Table A details the types of adaptations that may be possible and further information can be found in the MRC/DH/MHRA Joint Project document: 'Risk adapted approaches to the management of clinical trials of investigational medicinal products'.
- 5.2.2 Once developed the risk assessment and associated management and monitoring plans should facilitate a risk-proportionate approach to the trial activities.
- 5.2.3 The risk assessment document must be sent to the key members involved in the trial to request confirmation that they are in agreement before the document can be finalised. The risk assessment must be approved before Site Initiation Visit at the first site. Evidence of team review (e.g., meeting minutes and/or email correspondence) and the risk assessment must be stored in the TMF.
- 5.2.4 The risk assessment form must be version controlled in accordance with gSOP-39 Document Version Control and signed and dated by the Chief Investigator.

5.2.5 The Chief Investigator or delegated member of the project team is responsible for overseeing the mitigations or actions planned from the risk assessment. This must be documented in the TMF.

Table A: Possible adaptations depending on the risk of the study

	Type A	Type B	Type C
Reduced MHRA role in approvals	Yes (notification only)	No	No
Adverse Event/Reaction Recording & Reporting	Yes	(Yes)	(Yes)
SAE/SAR Reporting	(Yes)	(Yes)	(Yes)
SUSAR reporting to MHRA/REC/Concerned investigators	No	No	No
Annual Safety report	No	No	No
Requirement for Trial Level IMP accountability	Yes	(Yes)	No
Requirement for Subject Level IMP accountability	Yes	(Yes)	No
Storage condition records	(Yes)	(Yes)	No
Protocol deviation impact assessment	(Yes)	(Yes)	No
Requirement for Investigators Brochure	Yes	(Yes)	No
Requirement for IB annual update	No	No	No
Requirement for a Sample Label	Yes	(Yes)	No
Requirement for Certificates of Analysis	Yes	(Yes)	No
Investigational Medicinal Product (IMP) Shipment(s)	Yes	Yes	No
Instructions for Handling IMP(s)	Yes	(Yes)	No
Master Randomisation List	No	No	No
Decoding Procedures for Blinded Trials	No	No	No
IMP Accountability at Site	Yes	(Yes)	No
IMP Return &/or Destruction	Yes	(Yes)	No
Investigational Medicinal Product Dossier	Yes	(Yes)	No

Manufacturer's Authorisation for Investigational Medicinal Product (MIA IMP)	Yes	(Yes)	No
Manufacturer's Authorisation (MA)	(Yes)	No	No
Authorisation for IMP Importation	No	No	No
Qualified Person Certification	Not applicable	(Yes)	No
Statement of EU GMP or EU GMP Equivalence	Yes	(Yes)	No
Safety Monitoring Plan	No	No	No
Yes- possible; (Yes) – may be possible on case by case basis; No – little, if any flexibility in requirements			

5.3 Ongoing review

- 5.3.1 The risk assessment must be reviewed at least annually, or earlier if new information becomes available. For example after site initiation visit, a protocol amendment, or when the summary of product characteristics / investigator brochure is updated.
- 5.3.2 Evidence of the review (e.g., meeting minutes and/or email correspondence), must be documented in the Trial Master File (TMF) even if no changes are required.

6. RELATED DOCUMENTS

- gSOP-033 Risk Assessment
- [Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products](#)
- The MHRA Good Clinical Practice Guide "Grey Guide" p402, Published 2012

7. APPENDICES

- Appendix 1 - Definitions

8. AUTHORSHIP & APPROVAL

Author

Signature

Date

Pro-Vice Chancellor (Research & Enterprise) Approval

Signature

Date

9. VERSION HISTORY/REVISIONS

Version Number	Effective Date	Reason for Change

10. AGREEMENT (MOVE ON TO SEPARATE SHEET BEFORE PRINTING)

Please detach and retain within your training files

I have read and understood the contents and requirements of this SOP (ref gSOP-037-01) and accept to follow University policies implementing it.

<p>Recipient</p> <p>Signature:Date:</p> <p>Name & Position:</p>
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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 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.