Risk Assessment Process

Research & Development

Standard Operating Procedure for the Risk Assessment Process for CTIMPs

SOP Number : SOP-33-04	**Effective Date:** October 2021
Version Number: v04	**Review Date:** 2-3 years

1.0 BACKGROUND

This document sets out the procedures to be followed by all West Hertfordshire Hospitals Trust (WHHT) staff who are involved in the assessment of the risk and preparation of a risk assessment document for clinical trials managed or Sponsored by WHHT.

It provides guidance on the requirements for risk assessment.

For every Clinical Trial of an Investigational Medicinal 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.

2.0 PURPOSE

For use by research staff working on Clinical Trials of Investigational Medicinal Products (CTIMPs). The Risk Assessment is completed by R & D staff working in collaboration with research staff involved in the study. This SOP is specifically for CTIMPs, however in the absence of a documented procedure can be used as guidance for any other clinical study.

3.0 APPLICABLE TO

Any Trust employee involved with clinical research sponsored by WHHT including, Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Co-investigators, Clinical Trial Pharmacists, Research Managers, Statisticians, Research nurses, Allied Health Professionals, Trial Coordinators, R&D Department, the Research & Development Steering Group (RDSG) & Data Managers.

4.0 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 tasks to a competent member of the study team. This delegation should be on the Sponsor/Chief Investigator delegation log.

5.0 PROCEDURES

The following sections provide a description of the processes to be followed when performing a risk assessment for a CTIMP.

5.1 Items Required

- CTIMP Risk Assessment: Part 1
- CTIMP Risk Assessment: Part 2
- Risk Assessment
- Collaboration agreement
- SOP Start up Procedures

5.2 Considerations

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

5.3 Risk Assessment

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

5.4 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: ● 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 IMPs 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

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:

- Initial Risk Assessment
- Monitoring Risk Assessment
- Ongoing Risk Assessment

5.5 Completing the Risk Assessment: General Guidance

The Risk Assessment process has been split into two parts;

- Part 1 is confidential, is held by the R&D Department and is for information.
- Part 2 translates the remaining risks associated with the trial into an appropriate method and frequency of monitoring; this can be filed in the Trial Master File (TMF)
- The expertise of specific disciplines must be sought when completing both parts of the risk assessment (e.g. Radiology, Pharmacy etc)
- Each risk category will have a number of trial specific risks associated with it; these should be recorded in the 'Trial Specific Details' column
- Then use the initial risk assessment information to rate the likelihood and the consequences of the risk, use the WHHT risk assessment tool

5.5.1 **Part 1 - Initial Risk Assessment**

- This is a confidential document kept by the R&D Department with input from the R&D Steering Group (RDSG)
- This is then provided to the Associate Director of R&D who ensures that the final Risk Assessment is communicated to the Sponsor for information
- Considerations in this first stage of the Risk Assessment Process:
    - 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 (70 day timeline for first patient recruited – Time & Target)
- Study design
- Number of competing studies and patient population
- 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:

- CI/PI
- Clinical Trials Unit Staff – Clinical Trial Monitor, Statistician
- Sponsor's legal advice

Part 1 of the Risk Assessment is led by an appropriate member of R&D staff on behalf of the RDSG liaising with the CI.

- The first page is dedicated to study identification and the proposed study design, this section must be completed before the document is finalised
- The risk assessment confirms 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 R&D Office 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)
- Note that when completing the risk assessment tool assessment of the reference safety information that will be used should include how often this information should be updated
- Once part 1 is finalised it must be sent to the RDSG for review
- The approved copy should be filed in the in the Regulatory Oversight file and a copy provided to the Sponsor

5.5.3 **Completing Risk assessment Part 2**

This is an open document that is approved and a copy filed in the TMF.
The assessment has input from all stakeholders involved in the study:

- CI/PI
- CTU staff, Statistician

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.

Considerations in this second stage of the Risk Assessment Process:

- o Sections from the Sponsor Risk Assessment that could be considered public
- o Study design - procedures
- o Patient population

Document the assessment as Risk Assessment Part 2.
The Risk Assessment informs the creation of the 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 R&D Department and CI with reference to completed Risk Assessment Part 1, and in discussion with the assigned study monitor.

The 'monitoring requirements' section details:

- 'Method of monitoring' - whether a risk will result in monitoring that is done on-site, remotely or centrally via data management.
- 'Frequency of Monitoring' – e.g.: 3 monthly, 6 monthly or annually (or as determined with the study team depending on risk). This gives an indication of how often that a particular risk should be reviewed, for example a high risk that a participant could be entered onto the trial without informed consent will result in the consent forms being checked at every visit to ensure the newly enrolled participants can continue on the study in confidence.
- 'Monitoring Activity' – e.g.: Source Data verification, TMF review etc. This describes the specific activity that will be carried out as a result of the risk in order to minimise or mitigate it. For example Source Data Verification or review of medical notes for missing adverse events.

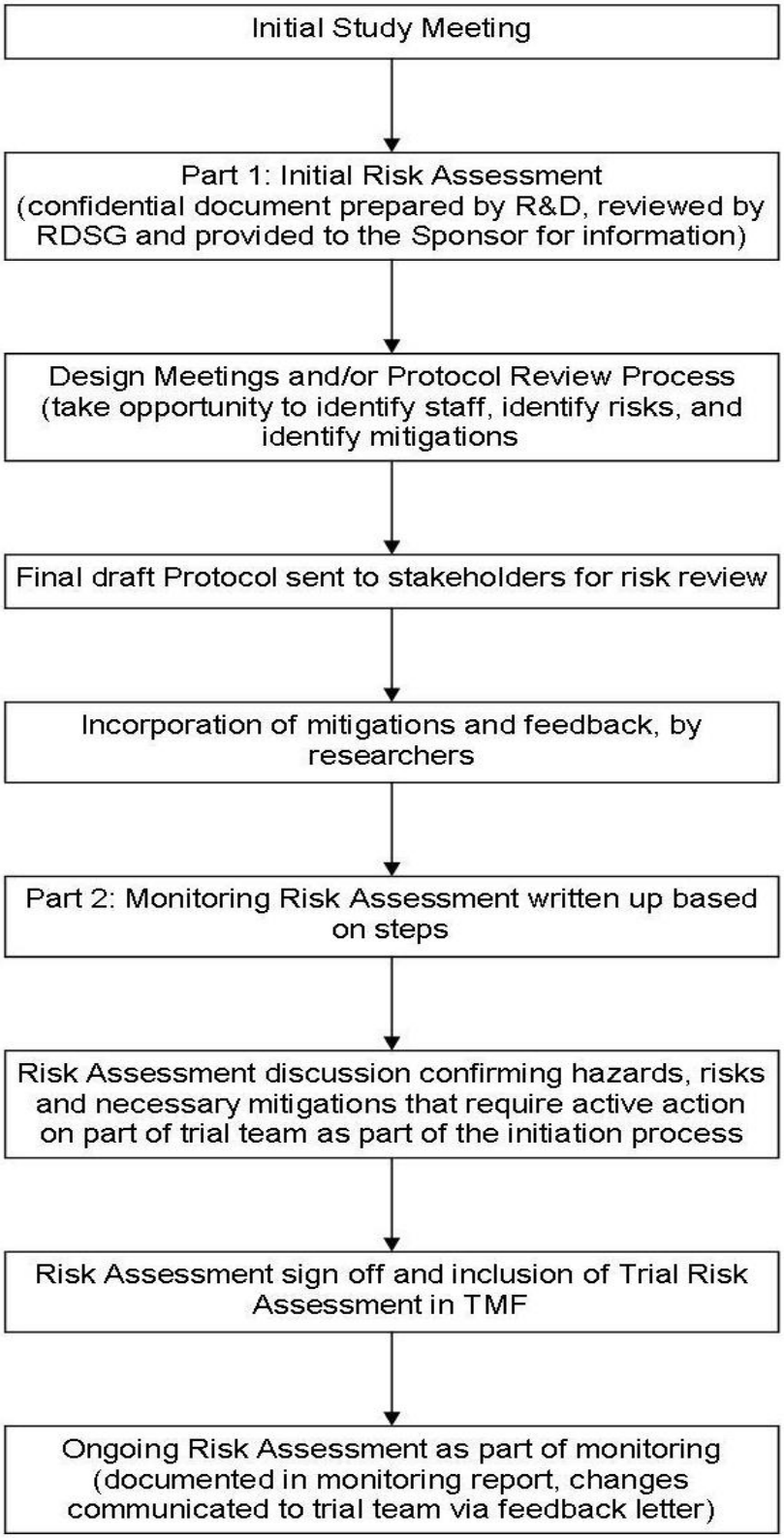
5.5.5 **Part 3 - Ongoing Risk Assessment during Monitoring**

- Ongoing risk will be recorded in the Monitoring Report Form for a given visit, and it will result in feedback to the research team if necessary
- This part of the monitoring report allows for ongoing comment on the risk assessment, and would also note any changes to monitoring frequency or practice due to findings, amendments or other triggers, some of which may be identified in the Monitoring Plan.
- The Monitoring Plan may be updated as a result of this ongoing risk assessment.
- Note: The frequency of monitoring is agreed based on the risk rating

5.5.6 **Change to the Risk**

- During the lifetime of the trial the risk rating may change
- New risk assessment documentation will be completed at any stage if it is deemed appropriate and reviewed by RDSG.
- Changes to the risk that affect the monitoring frequency will be recorded in the trial monitoring reports and communicated to the Sponsor and trial team via the monitoring feedback letters

5.5.7 **Process Flow**



5.6 Compliance Monitoring

5.6.1 **Process for Monitoring Compliance**

As part of routine monitoring visits, audit and inspection.

5.6.2 **Standards/Key Performance Indicators**

This process forms part of a quality management system. Documents are reviewed every two to three years.

6.0 RELATED 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

7.0 APPENDICES

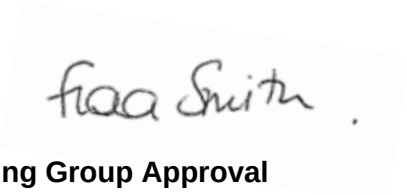
Appendix 1 - Definitions

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
SOP-33-04	**October 2020**	1. Change from general Standard Operating Procedures (gSOP) to SOP 2. Removal of the ‘10.0 Agreement’ from the template - all agreement signatures will be collated on a new ‘SOP Signature Sheet Document’ 3. Other minor changes and clarifications of terms following review
gSOP-33-03	**October 2017**	Minor amendments following review

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date** 28/10/2021

R&D Steering Group Approval

Signature  **Date** 28/10/2021

Appendix 1: Definitions

Adverse Event (AE)
An unfavourable outcome that occurs during or after the use of a drug or other intervention, but is not necessarily caused by it.

Chief Investigator (CI)
The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI.

Clinical Trial
A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. A Study Type.

Clinical Trial of Investigational Medicinal Product (CTIMP)
A clinical trial that is within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. An investigation in human subjects, other than a non-interventional trial, intended: a) to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, b) to identify any adverse reactions, or c) to study absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products.

Investigational Medicinal Product (IMP)
A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a Clinical Trial, and includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial - a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation, b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or c) used to gain further information about the form of that product as authorised under the authorisation.

Monitoring
The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted and recorded in accordance with the protocol, Standard Operating Guidelines (SOP's), Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

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

Principal Investigator (PI)
The investigator responsible for the research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person.

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)

The MHRA is the competent authority for the UK in relation to the Directive 2001/20/EC and the Clinical Trials Regulations, and for Medical Devices, the competent authority in relation to the Medical Devices Regulations 2002.

Trial Management Group (TMG)
The Trial Management Group normally includes those individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, statistician, trial manager, research nurse, data manager. 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 contains all essential documents held by the sponsor/Chief Investigator which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced.

Type A Clinical Trial
Trials with no higher risk than that of standard medical care.
Trials involving medicinal products licensed in any EU Member State if:

- They relate to the licensed range of indications, dosage and form.
- Or, they involve off-label use (such as in paediatrics and in oncology etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines.

Type B Clinical Trial
Trials with somewhat higher risk than that of standard medical care
Trials 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.

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
Trials with markedly higher risk than that of standard medical care.
Trials involving a medicinal product not licensed in any EU Member State.