# Clinical Trial Risk Assessment for High Risk, NuTH Sponsored Trials

**NJRO-REG-SOP-004**

## Contents

## 1. Background/Introduction

1.1 All high risk clinical trials requesting sponsorship by The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) must undergo a risk assessment to identify the potential risks and hazards of the trial. The risk assessment should be performed at an early stage of protocol development so that any required modifications to mitigate hazards can be incorporated into the trial.

1.2 The risk assessment represents a 'living' document that should be reviewed at least annually and updated throughout the life cycle of the trial where appropriate. This reflects the nature of potential risks/hazards which may differ in response to trial proceedings e.g. substantial amendments, protocol violations, serious breaches, monitoring visit outcomes, trends in serious adverse events (SAEs) and audit findings etc.

1.3 The Department of Health, the Medicines and Healthcare Products Regulatory Agency (MHRA) and Medical Research Council joint risk-stratification project stated: 'For every trial there is a core set of risks inherent to the protocol that relate to the safety of the participants and the integrity/reliability of the results. All organisations involved need to understand these risks so that the control measures, resources, procedures and processes implemented during the trial ensure the safety of the trial participants, and lead to high quality results'. They initiated the concept of risk-adapted approaches to the management of clinical trials. Their intention was to simplify the processes for initiating and conducting clinical trials with IMPs.

1.4 In June 2017 the guideline for Good Clinical Practice E6 (R2) addendum to 'Section 5: Sponsor' formalised the requirement for Sponsors to have processes in place to identify, evaluate, control, communicate, review and report risk:

1.4.1 Risk identification; Sponsors should identify risks to critical trial processes and data. These risks should be considered at both system level (e.g. personnel, e-systems, standard operating procedures etc.) and at a clinical trial level (e.g. trial design, informed consent procedures etc.).

1.4.2 Risk evaluation; Once identified these risks should be evaluated considering:
the likelihood of errors occurring;
the extent to which they would be detectable;
the impact upon human subject protection; and
the reliability of results.

1.4.3 Risk control; Sponsors must decide which risks to reduce and/or which to accept. The approach to reduce risk should be proportionate to the significance of the risk. Predefined quality tolerance limits should also be established and deviations from these limits should trigger an evaluation to determine if action is required. The quality tolerance limits will be determined on a trial by trial basis considering the medical and statistical characteristics of the variables as well as the statistical design of the trial in

order to identify systematic issues that can impact subject safety and the reliability of trial results. Examples of quality tolerance limits may relate to a disproportionate number or trend in SAEs, characteristics of protocol violations/serious breaches and findings from monitoring/audit reports, all of which should be pre-defined within the monitoring plan prior to trial initiation.

1.4.4 Risk communication; Sponsors should document quality management activities. This will be documented and communicated in various forms, including but not limited to audit plans, monitoring plans, trial oversight structures, safety reporting systems, data management plans, deviation logs, and Sponsor oversight committees (e.g. Clinical Trials Unit (CTU) oversight meetings and appropriate senior management meetings). These should be communicated to those involved in or affected by such activities in order to facilitate risk review.

1.4.5 Risk review; periodic review of risk control measures, taking into account emerging knowledge and experience, should be performed to ensure quality management activities remain effective.

1.4.6 Risk reporting; Sponsor should describe the quality management approach implemented in the trial and summarise important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report.

1.5 All of the following trial categories (defined as 'high risk') requesting sponsorship by The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) must undergo a risk assessment at an early stage of study development. Risk controls must then be put in place using risk adaptive and risk proportionate approaches.

1.5.1 Clinical Trials of Investigational Medicinal Products (CTIMPS)

1.5.2 Advanced Therapy Investigational Medicinal Products (ATIMPS)

1.5.3 Clinical Investigations of medical devices without a CE mark or devices being used outside of their CE marking

1.5.4 Randomised surgical trials

1.5.5 Multicenter International Studies (where required)

1.6 It is the responsibility of the Sponsor (Regulatory Compliance Manager (RCM) or an appropriate delegate) to complete the risk assessment, although this task is often delegated to the Chief Investigator (CI) with input from the trial management team. Nonetheless, despite the completion of the risk assessment being an ongoing collaborative process, the final decision with regards to risk categorisation lies with Sponsor.

## 2. Purpose

This Standard Operating Procedure (SOP) describes the process of risk assessment that must be performed for all high risk research studies requesting sponsorship from NuTH that fall under the Regulatory Compliance Team. All other medium and low risk NuTH sponsored trials may undergo a risk assessment during sponsorship review, the depth of which will vary depending on the initial perceived risk.

## 3. Scope of Document

This SOP applies to:

- All investigators requesting sponsorship from NuTH for high risk research studies.
- Those members of the Newcastle Joint Research Office (NJRO) with responsibility for reviewing projects for NuTH sponsorship but primarily the Regulatory Compliance Team.
- This SOP is also applicable to personnel of Clinical Trials Units, trial management and project management teams who have been contracted by the Chief Investigator (CI) to set up and manage the trial.

## 4. Definitions

**Hazard:** any source of potential damage, harm or adverse event.

**Risk in a clinical trial**: 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**: a process of identifying the potential hazards associated with a trial, and assessing the likelihood of those hazards occurring and resulting in harm.

**Risk adaptive approach**: relies on a risk-stratification process in relation to how much is known about the medicine(s) being investigated. Categorising the risk associated with the Investigational Medicinal Product (IMP) allows for risk adaptations/simplification within the scope of the Clinical Trials Directive.

**Risk proportionate approaches**: Trial monitoring is not a standardised activity that must be implemented in an identical way in all trials. The risk assessment process allows structured review of the vulnerabilities associated with the trial design and methods thereby identifying the main risks in the trial. This enables the development of trial-specific, targeted and proportionate strategies and monitoring plans.

**Risk mitigations**: strategies or procedures that reduce either the impact or the

probability of an adverse consequence of a hazard.

## 5. Roles & Responsibilities

The Regulatory Compliance Team on behalf of Sponsor are responsible for ensuring that a risk assessment is completed during the protocol development stage and that this is reviewed at least annually and updated in response to all relevant trial proceedings (e.g. applicable substantial amendments, serious breaches etc.).

Where appropriately delegated via the Sponsor Delegation of Duties Agreement, the CI and trial management team are responsible for populating the Sponsor risk assessment template and submitting this to the Regulatory Compliance Team for review.

The CI and trial management team are also responsible for updating the risk assessment in relation to relevant trial proceedings and submitting any updates to Sponsor for review.

The Regulatory Compliance Team (Sponsor), CI and trial management team are all responsible for reviewing and signing off the completed risk assessment (along with any updates).

## 6. Procedures

The Regulatory Compliance Team (RCT) act on behalf of NuTH in response to requests for sponsorship of CTIMPs, ATIMPs and high risk clinical trials. An initial high level risk assessment with an agreement to provide provisional Sponsorship must be obtained from the Regulatory Compliance Manager (RCM) or an appropriately trained delegate at the time of the funding application. To allow for funding application costing, the Sponsor will input in to risk categorisation discussions at the funding application stage. This risk categorisation will be reconfirmed as part of this SOP process.

As soon as possible after funding has been confirmed, and when sufficient information is available, the risk assessment process described in this SOP must commence.

The RCM (or delegate) will initiate completion of the clinical trial risk assessment form (CTRAF - parts A & B) by the CI and trial manager (see associated document: NJRO-REG-T-001). The Sponsor will request the CI and trial management team to complete the CTRAF (parts A & B) and then return the draft version to the Sponsor management inbox (tnu-tr.sponsormanagement@nhs.net) for Sponsor review/comments.

Once Sponsor's comments have been addressed, the CTRAF must be finalised, approved and signed off **BEFORE** protocol sign off or final submission of trial documentation to the MHRA, REC and HRA.

For trials managed by a Clinical Trials Unit (CTU), it is acknowledged that alternative risk assessment templates may be used pending review/agreement from the sponsor team. If alternative templates are to be used, these must be completed and submitted to sponsor for review and comments as per the above.

Where alternative risk assessment templates are used, a sponsor appendix may also be completed to document any sponsor level risks (NJRO-REG-T-026), and this will be attached to the overall risk assessment for the trial.

6.1 Risk Identification

When completing the CTRAF, the CI and/or trial manager should start by considering the potential hazards for the trial with respect to the following areas:

**Part A** - IMP/Intervention risk category and safety monitoring plan

- Risk to participant safety associated with the intervention(s) being used

**Part B** Risks associated with the design and methods of the trial

- Risks associated with the design and methods of the trial
  - Risks to participants
  - Risks to reliability of results
- Organisational Hazards (examples include resources (HR, equipment); financial; vendor availability/capability etc.).

**Part A**: The risks to participants associated with the interventions under investigation should be assessed in relation to standard care for the patient group concerned and the level of knowledge regarding the effects of the interventions:

Table 1: Clinical Trial Risk Categorisation (see Appendix 8.1)

| Risk Category | Definition |
|---|---|
| Type A | Comparable to the risk of standard medical care |
| Type B | Somewhat higher than the risk of standard medical care |
| Type C | Markedly higher than the risk of standard medical care |

The risk category of the trial interventions will guide the nature and extent of patient safety monitoring that will be required in the trial. Examples of specific aspects to consider are the nature of IMP, potential toxicities, the body systems to be affected and the type and frequency of intended monitoring (which will be documented within the initial monitoring plan). Further examples are provided in the 'CTRAF – Part A' section of NJRO-REG-T-001, although please note that this list is not exhaustive.

Completion of Part A will enable Sponsor to determine what specific risk adaptations are suitable for various aspects of the trial. Any adaptations will be captured throughout the risk assessment and study protocol.

**Part B:** Risks can also arise from the protocol and study related procedures. These include risks to participants associated with clinical protocol related procedures, informed consent, personal data protection and also risks regarding the reliability of results.

In order to identify such risks, the CI, trial management team and the Regulatory Compliance Team on behalf of Sponsor should review the protocol to identify any of these areas where the risk is increased. Potential hazards should then be identified and an appropriate mitigation, management and optimal monitoring strategy should be established. This should be documented within the CTRAF in section Part B (see NJRO-REG-T-001).

Where alternative risk assessment templates are used (with approval from sponsor), the above aspects/risks should still be covered, and this will be assessed as part of the sponsor review.

6.2 Risk Evaluation

Once the hazards have been identified, the risk associated with each hazard should be assessed and compared against the hazards and risks of the equivalent standard clinical care.

There are 3 major questions when identifying risk;

1) What might go wrong?

2) What is the likelihood it will go wrong?

3) What are the consequences?

When Parts A and B of the CTRAF have been drafted (or alternative template drafted as approved by sponsor), the risk assessment should be sent to the Regulatory

Compliance Team via the Sponsor Management Inbox: tnu-tr.sponsormanagement@nhs.net for review.

The Regulatory Compliance Team will review and provide feedback as necessary. Discussion and finalisation of the CTRAF (or alternative risk assessment template) should be included on the Trial Management Group (TMG) agenda until such time as it is finalised but this must be **BEFORE** protocol sign off or final submission of trial documentation to the MHRA/REC/HRA.

6.3 Risk Control

Each category is reviewed to determine the risks which could affect subject safety, data integrity or regulatory compliance.

A risk level (high, medium, or low if using the CTRAF) is then determined for each category.

The Regulatory Compliance Team (Sponsor), CI and trial management team collaboratively decide which function(s) will manage the risk, with input from any relevant functional areas (e.g. Pharmacy, Quality Assurance (QA) etc.).

This overall risk is used to determine the baseline monitoring approach and activities to be used for the protocol.

Any possible mitigation strategies for minimising/avoiding risk should be documented against each individual hazard. Particular consideration must be given to appropriate risk based monitoring and audit strategies. Input should be sought from other parties as appropriate to their role in the trial e.g. NJRO, CI, the relevant CTU or Sponsor Pharmacy.

The extent and nature of monitoring must be determined prior to the start of the trial and be re-assessed during the course of a trial. The clinical trial risk assessment may be used to determine the **intensity** and the **focus** of the monitoring activity, whilst the trial design would inform the **methods** used for monitoring. Assessment of the sites, staff facilities and training needs may also influence the intensity and nature of the monitoring methods (this should be reflected within the monitoring plan for the study – see NJRO-GEN-SOP-021).

6.4 Risk Communication

On finalisation of the CTRAF (or alternative risk assessment template), it should be documented in the TMG meeting minutes who must be included in the circulation of the finalised risk assessment. This also applies to all amendments made to the risk assessment throughout the lifecycle of the trial.

6.5 Risk Review

Review of the risk assessment must be included as a standing agenda item at the TMG meetings so that the risk assessment is re-visited periodically over the life-time of a trial and takes into account new information and issues that become apparent after the start of the study. As a minimum the risk assessment must be reviewed annually in line with the Development Safety Update Reports (DSUR) if applicable.

In addition, the risk assessment should be reviewed under the following circumstances:

- Following a serious breach of Good Clinical Practice
- Following a violation of the protocol (or a relevant emerging trend in protocol deviations)
- If a substantial amendment is made that results in a change to protocol procedures
- If the benefit/risk assessment for the intervention/trial changes
- Following any necessary updates to the reference safety information
- If changes are required to the trial monitoring plan
- If substantial changes to the PIS, ICF or case report forms (where appropriate) are needed
- In response to appropriate monitoring/audit findings (as deemed necessary by the RCT)
- In response to significant changes in routine/clinical care that may impact the clinical trial.

The 'Continuous Risk Assessment Review' form (see NJRO-REG-T-003) should be used to document any reviews of the CTRAF (or alternative risk assessment template); although if no changes are deemed necessary, this review may be documented via email. The CTRAF review will be completed by the Regulatory Compliance Team with relevant input from the CI, trial management team and any other relevant stakeholders.

In response to a substantial amendment, completion of the 'Continuous Risk Assessment Review' form may be delegated to the trial management team as appropriate.

The 'Continuous Risk Assessment Review' form should be signed by the Sponsor and any relevant contributors. Where an update to the overall risk assessment is required, the completed 'Continuous Risk Assessment Review' form should be sent to the CI for comments and acknowledgement.

6.6 Risk Reporting

The Monitoring Plan should provide an overview of the monitoring and audit activities. It should summarise important deviations from the predefined quality tolerance limits which will be determined on a trial by trial basis. Examples of such deviations may include a disproportionate number or trend in SAEs, protocol violations or serious breaches etc. In order to effectively respond to such deviations, the monitoring plan should also document the point at which Sponsor would intervene by. As a result of this, Sponsor actions may include the request of additional monitoring, the request of an audit by Sponsor or the NJRO QA team, informing the Clinical Director of Research & Development (R&D), the request of a temporary/permanent halt to activity, and/or informing the MHRA and/or REC of concerns. Any remedial actions taken should be documented accordingly.

6.7 Responsibilities

It is a delegated responsibility of the CI to ensure that the risk assessment is completed as part of the development of the protocol although representatives of the Sponsor and relevant CTU personnel will also contribute to the content of the form.

The risk assessment should fully inform the individual monitoring and audit requirements.

6.8 Risk-based Monitoring

The risk assessment should fully inform a systematic, prioritised, risk-based approach to the monitoring of clinical trials. This is intended to permit varied approaches to monitoring in order to improve its effectiveness and efficiency.

For instance, the monitoring plan may incorporate the use of:

- On-site Monitoring: monitoring performed at the sites at which the trial is being conducted
- Centralised (remote) monitoring: remote evaluation of accumulating data performed in a timely manner.

Centralised monitoring can provide additional monitoring capabilities that complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable and unreliable data in a timely manner. For instance, accumulating data from centralised monitoring can be used to identify missing / inconsistent data; identify protocol deviations; examine data trends within and across sites; evaluate for systematic errors in data collection and reporting (including data manipulation and integrity); analyse metrics; and identify sites requiring targeted on-site monitoring.

However, the rationale for selecting a particular monitoring strategy (i.e. whether this is solely on-site monitoring, centralised monitoring or a combination of the two) should be fully outlined in the monitoring plan and should be fully informed by the risk assessment. Both the risk assessment and monitoring plan should be stored in the Trial Master File (TMF) and Sponsor Oversight File (SOF).

## 7. References

MRC/DH/MHRA Joint Project: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, version: 10th October 2011

ECRIN Risk-Adapted Monitoring in Clinical Trials

MHRA Good Clinical Practice Guide (2012)

Indexed ICH GCP Guidelines with Integrated Addendum E6(R2); Step 4; November 2016.

## 8. Appendices

8.1 Clinical Trial Risk Categorisation Table

Appendix 8.1 – Clinical Trial Risk Categorisation Table

| CATEGORY | LEVEL OF RISK | CTIMP or ATIMP | SURGERY | MEDICAL DEVICE |
|---|---|---|---|---|
| **A** | No or minimal risk over that of standard clinical care | • Trial of a licensed product being used within its marketing authorisation.<br>• Off-label use of a product if this is established practice e.g. in paediatrics or oncology. | • Minimally invasive technique.<br>• Technique/biopsy performed on internal organ | • Trial of a CE marked device being used within its licensed indication.<br>• Trial of a class I or IIa CE marked device used outside of its licensed indication. |
| **B** | Minor increase in risk over that of standard care | • Trial of a licensed product in an unlicensed indication/new combination.<br>• Trial of a licensed product with substantial dose modifications. | • Generalisation of a new technique. | • Trial of a class IIb CE marked device being used outside of its licensed indication. |
| **C** | Significant increase in risk over that of standard care | • Trial of an unlicensed product. | • Development of a new technique. | • Trial of a class III CE marked device being used outside of its licensed indication.<br>• Trial of a device without a CE mark. |