

SOP number	51.004	Version	6.0
Title	Risk Assessment for CTIMPs and CIMDs Sponsored by NHS Greater Glasgow and Clyde (NHSGGC), or Co-Sponsored with the University of Glasgow (UoG)		

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SOP category	NHSGGC Sponsor R&I			
Staff Category	R	A	C	I
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R&I Systems and Operations Manager	X			
Sponsor Research Coordinators (SRC)	X			
Sponsor Innovation Coordinators (SIC)	X			
R&I Pharmacy	X			
R&I Clinical Trials Monitors	X			
R&I Pharmacovigilance (PV) Officer	X			
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Project Managers	X			
Chief Investigators	X			
Study data managers	X			
Study Statisticians	X			

1. Scope

This procedure applies to Clinical Trials of Investigational Medicinal Products (CTIMPs) and Clinical Investigations of non-CE marked medical Devices (CIMDs) sponsored by NHS Greater Glasgow and Clyde (NHSGGC) or co-sponsored by NHSGGC and the University of Glasgow (UoG).

2. Purpose

The purpose of this SOP is to describe the procedure for risk assessment of CTIMPs or CIMDs sponsored by NHSGGC or co-sponsored with the UoG. The aim is to ensure that all relevant stakeholders, with a range of expertise in clinical research, systematically identify and evaluate potential areas of risk associated with the overall conduct of the trial as described in the protocol and in line with current regulations and whether, or how, these risks can be mitigated. This process is designed to minimise risk to participants safety, patients' rights, data integrity, and ensure regulatory compliance.

3. Procedures

3.1. Background

Risk assessment in clinical trials is essential to protect participant safety and ensure data integrity, as required by ICH-GCP. The MHRA expects that critical to quality factors should be implemented. These should be defined prior to/alongside protocol development. These should be integrated into the trial protocol, risk assessments, quality plans, data management plans etc., so that they are transparent and considered cross-functionally

A hazard is a potential source of harm. Risk in a CTIMP refers to the likelihood of that hazard occurring and the gravity of its potential impact on trial participants, the Sponsor(s), or the reliability of the data.

The Risk Assessment process involves:

- identifying hazards/risks
- evaluating their likelihood and potential impact
- proposing mitigation strategies to eliminate, reduce, or accept them

The MHRA categorises Clinical Trials as either:

- Notifiable trials (low-risk CTIMPs that do not require explicit MHRA authorisation before starting and meets the requirements of Regulation 11A of the Medicines for Human Use Clinical Trials Regulations.).
 - These typically involve:
 - UK-licensed medicines
 - Used within (or very close to) marketing authorisation
 - No significant additional safety concerns
 - Trial may automatically proceed if MHRA does not raise concerns within the notification period.
- Trials requiring full authorisation by the MHRA before they can start
 - These include trials:
 - Involving unlicensed IMPs
 - Using licensed medicines outside their authorised indicated, dose, or population with potential safety impacts
 - First in-human or higher risk designs

These categorisations replace the previously categorised Type A, B and C (Notifiable Trials replacing most Type A and Authorised Trials replacing Type B and C – there is no longer a formal distinction between B and C in legislation – risk is assessed based on the individual trial).

This categorisation may inform the level of oversight and type of monitoring required (e.g. onsite, central, remote) and whether oversight committees should be put in place (e.g. Independent Data Monitoring Committee, Trial Steering Committee, Safety Review Committee). The final decision on the level of these activities will still be determined by the individual risk profile of the trial.

The MHRA categorisation for trials involving an IMP does not apply to Clinical Investigation of a Medical Device (CIMDs), instead the device's risk class (as per Medical Devices Regulations 2002, as amended), is recorded.

MHRA Guidance on this can be found here: <https://www.gov.uk/guidance/clinical-trials-for-medicines-guidance-on-quality-and-risk-proportionality>.

If a trial involves both an IMP and CIMD both risk categorisations will be documented.

3.2. Assessment of Risk for a Clinical Trial

The risk assessment process is an ongoing activity throughout the lifecycle of a trial. Initial identification of risks may begin as soon as NHSGGC becomes aware of a trial and recorded on Form 51.010E: R&I Study Strategic Plan, at grant stage. However, the formal risk assessment meeting using Form 51.004A: Risk Assessment Tool occurs when a reasonably complete version of the protocol is available, before the submission of the study to REC and MHRA, allowing mitigations to be included in the protocol where possible. Form 51.004E (Risk Assessment Mitigations Tracker) will be completed by the SRC/SIC at this time for all mitigations, including those that cannot be completed prior to regulatory submissions.

As a living document, the Risk Assessment Tool will be reviewed when required e.g. during significant protocol modifications, after protocol deviations, serious breaches or upon receipt of new relevant information and as a practical experience accumulates during the trial. Systems and processes must allow for the continued assessment of critical to quality (CTQ) factors and related risks with appropriate risk control and mitigation applied where indicated. Therefore, the Risk Assessment Tool and Risk Assessment Mitigations Tracker will also be reviewed on an ongoing basis at Trial Management Group (TMG) Meetings to ensure ongoing, dynamic risk review, throughout the trial lifecycle.

The Sponsor Research Co-ordinator/ Sponsor Innovation Co-ordinator (SRC/SIC) manages the Risk Assessment process, involving a multidisciplinary team including, but not limited to, the Chief Investigator (CI), the study team, a pharmacist, the assigned Clinical Trial Monitor (CTM) +/- Lead CTM, Pharmacovigilance (PV) Manager +/- PV Officer, Project Manager (PM), Statistician, Data Manager (DM), NHSGGC Research Governance Manager and UoG Sponsor representative (for co-sponsored trials). The Robertson Centre for Biostatistics stakeholders that must be involved are part of the Data Centre Team and should include (when applicable) PM, Statistician, DM and/or System Developer.

3.3. Critical to Quality Factors (CTQ)

A Critical to Quality Factor is a trial attribute, process, data element or activity that is fundamental to the protection of participant rights, safety and wellbeing, or to the reliability, integrity and interpretability of trial results. Critical to Quality Factors (CTQ) are addressed through the risk assessment and potential CTQ factors are suggested with the existing heading outlined in Form 51.004A and Guideline 51.004A to cover the majority of areas to be considered as outlined in ICH E8 (R1). As each trial is unique, additional CTQ factors will be identified on a trial-by-trial basis and must be flagged during this process. An appropriate mitigation for CTQ factors may be to introduce Key Risk Indicators or Quality Tolerance Limits. This will cover key data such as consent, eligibility, safety, primary and secondary endpoints and any other data critical to safety and reliability of results such as window compliance.

3.3.1. Signal Detection

Signal detection is the systematic process for looking for any new or changing safety data that could alter the known risk-benefit profile of the IMP. The following areas will be covered through the risk assessment process to identify the factors critical to the safety of participants and the reliability of the data. If the study set up does not allow for signal detection this should be documented within the risk assessment with the reasons why and risks this may pose.

- Adverse Events and Adverse reactions- consider whether all non- serious AEs need regular review. The aim is to look for an unexpected increase in the frequency or severity of known, non-serious adverse reactions
- SAEs and SUSARS- review all SAEs, SARs and SUSARS- Immediate and aggregate evaluation of this data and whether a focus on designated medical events is required.
- Laboratory Findings and Diagnostic trends- review of biochemical, haematology, urinalysis, specialised tests. This focuses on target organ toxicity thresholds
- Vital signs and Physical Findings-blood pressure, heart rate , ECG, cardiac monitoring. The focus here is on aggregate shifts in the population.
- Specific populations- This may include pregnancy monitoring and drug interactions with concomitant medications.
- Lack of Efficacy Data – rates of disease progression or treatment failure
- Extrapolated External Data- This may include preclinical data, data from other trials to ensure up to date information is included in safety assessments.

3.4. Overview of Assessment Process

Prior to the first formal risk assessment meeting, the SRC/SIC must seek input from all stakeholders to develop a draft of Form 51.004A and record specific areas of risk to be discussed. Guidance Document GUI 51.004A should be used when completing Form 51.004A. This draft, alongside the current protocol and other available study documentation as required (e.g. patient information sheet(s)/consent form(s)), will be shared for comment ahead of the meeting.

During the formal Risk Assessment meeting, using Form 51.004A, Guideline GUI 51.004A, relevant legislation and MHRA guidance to inform decisions, stakeholders will:

- agree risk categorisation for CTIMPs or device classification for CIMDs, along with justification
- identify risks, their impact and likelihood, and proposed mitigations

All contributions to the risk assessment will be recorded on Form 51.004A. If a risk cannot be mitigated, this will be documented along with the Sponsor's rationale for accepting it.

3.5. Categorisation of Trial Type

3.5.1. CTIMPs

The categorisation defined in MHRA guidance will be discussed and agreed at the risk assessment meeting. The categorisation will be recorded in Form 51.004A.

The trial must meet a variety of criteria as outlined in regulation 11A of the Medicines for Human Use Clinical Trials Regulations to be classified as a notifiable trial.

3.5.2. CIMDs

Medical Devices are categorised to one of four classes based on the risk that a device poses to patients and user (as per Medical Devices Regulations 2002, as amended):

- Class I - Low risk (e.g. bandages, non-invasive software, examination lights)
- Class IIa - Medium risk (e.g. Hearing aids, suture needles, diagnostic software)
- Class IIb - Medium to high risk (e.g. infusion pumps, ventilators, surgical lasers)
- Class III - High risk (e.g. pacemakers, joint implants, implantable devices)

Risk classification determines:

- Level of clinical evidence needed
- Whether a UK Approved Body is involved
- Nature of post-market surveillance

Classification is determined by the Manufacturer of the device, often with MHRA guidance and this will be documented on the Risk Assessment Tool (51.004A).

3.5.2.1. In Vitro Diagnostic Medical Devices (IVDs)

IVDs (e.g. diagnostic tests, analysers) are classified separately, under the UK IVD framework, broadly aligned with the EU IVDR risk model.

IVD risk classes are as follows:

- Class A – lowest risk (e.g. specimen receptacles)
- Class B
- Class C
- Class D – highest risk (e.g. blood screening assays)

IVDs used in NHS research must be classified even if not being commercialised.

3.5.3. Combination of both CTIMP/CIMD

Both sections 3.4.1 and 3.4.2 will apply.

3.6. Risk Assessment Sections

Form 51.004A is comprised of four main sections, each with sub-sections to facilitate discussion:

- Risk to participants
- Risk to scientific integrity
- Risk to management
- Other risk (captures any additional risks not covered elsewhere)

Further guidance available in Guideline 51.004A: Clinical Trial and Medical Device Risk Assessment Guidance Document.

Each risk will be a separate row on the risk assessment tool. If a risk is deemed low, the Risk assessment tool will state whether any mitigation will be required. Medium and high risks will always have a mitigation strategy and an individual identified to mitigate with a timeframe. Some risks may not need to be dealt with prior to regulatory submissions, and this must be documented. Any risks that cannot be mitigated prior to RGL require to be agreed by all stakeholders. All mitigations will be tracked via the Risk Assessment Mitigations Tracker (Form 51.004E).

3.7. Completing the Risk Assessment Tool

Form 51.004A will document the hazards/risks identified, the likelihood of them occurring, the potential impact and the mitigation strategies. Where mitigation is not possible, this will be recorded with justification.

3.7.1. Perceived Risk

All stakeholders, guided by the SRC/SIC, are responsible for identifying perceived risks. Prompts are provided within Form 51.004A with additional detail available in Guideline 51.004A. All potential perceived risks must be considered and should not be limited to the prompts. If a risk has been identified, documented and appropriately mitigated in existing study documentation, it does not need fully detailed in Form 51.004A, instead the documentation/evidence must be referenced here.

Genetically Modified Organism GMO trials also require specific risk assessment of the GMO, focusing on the potential of the GMO to cause harm, the methods of modification and environmental impact (reviewing laboratory and preclinical work by the owner of the IMP) in accordance with the 'Guidance Notes for Risk Assessment' outlined in the Genetically Modified Organisms (Contained Use) Regulations 2014. The owner of the IMP may not be NHSGGC however the risk assessment will document who has this responsibility.

All participating locations are checked to ensure they are registered with the HSE (Health and Safety Executive) to undertake trials involving GMOs and that they have undertaken separate GMO risk assessments. Assessment of HSE registration is undertaken as part of the Location Capability Assessment (SOP 56.007/Form 56.007A). Where GMO activities are proposed, completion of a local GMO risk assessment is verified as part of the Location Green for Go process (SOP 56.001).

3.7.2. Likelihood

Likelihood of each risk occurring is assessed and recorded as Low/Medium/High. This will be dependent on any controls that are already in place e.g. SOPs, contracts. These controls should be documented on Form 51.004A. This is a pragmatic judgement to support planning (e.g. the level of monitoring and pharmacovigilance requirements) and does not require formal quantitative analysis. This assessment is the likelihood before any mitigation actions are put in place.

3.7.3. Impact

Impact is assessed and recorded as Low/Medium/High, based on the severity of potential consequences if the risk materialised. This is also an assessment before mitigations are put in place and before any action is taken to reduce the impact.

3.7.4. Risk Mitigation Strategies

Mitigation strategies are actions that aim to eliminate or reduce a risk. Stakeholders and sponsor representatives will collectively propose feasible mitigation actions. If no mitigation is possible, this will be documented in form 51.004A, along with the rationale for accepting the risk.

3.6. Management of Mitigation Actions

Mitigation actions recorded in the Risk Assessment will be listed by the SRC and assigned to stakeholders or their delegates for implementation. This will be reviewed by the SRC prior to Regulatory Green Light (RGL) being issued (SOP 51.020). All actions should be completed prior to issue of the Regulatory Green Light unless a longer timescale has been agreed and documented in the Risk Assessment (see Section 3.5), in which case these will be tracked on the Risk Assessment Mitigations Tracker (Form 51.004E) which will be reviewed on an ongoing basis via the Trial Management Group (TMG).

3.7. Review and authorisation

The completed draft of the Risk Assessment will be shared with all relevant stakeholders for any further review and comment prior to the first meeting. Additional meetings may be arranged as needed to resolve any additional issues.

Once the SRC/SIC, CI and all relevant stakeholders agree the initial Risk Assessment tool accurately reflects the identified risks and agreed mitigation strategies, the form will be labelled as Version 1, dated, and will be signed by all relevant stakeholders who have contributed to the risk assessment as well as the SRC/SIC as Sponsor representative and the CI. This authorised version of the document will then be shared with all relevant stakeholders and filed in the Trial Master File (TMF) as per SOP 51.016, and the Senior Research Administrator (SRA) will update SReDA accordingly.

For First-in-Human (FIH) trials or trials involving a GMO, the standard risk assessment process (described in this SOP 51.004) will be carried out. In addition, the Research Governance Manager and Sponsor Pharmacist must also review and sign Form 51.004A.

3.8. Updates to the Risk Assessment

Throughout the life cycle of the trial, it may be necessary to re-assess the level of risk e.g. when modifications to the study need to be made in response to multiple non-compliances, a Serious Breach, modifications or new information that impacts the trial.

When a substantial modification to the trial is required, the process outlined in SOP 51.021 will be followed. As part of this SOP, the Risk Assessment will be reviewed and, if needed, will be updated to capture new risks and mitigations. This will be documented using the Update to Risk Assessment form (Form 51.004D) and any new mitigations will be added to the Risk Assessment Mitigations Tracker (Form 51.004E). This will be populated and reviewed as described above for the original Risk Assessment, although this may not require input from all stakeholders. All contributors will be listed on Form 51.004D. If no additional hazards or risks are identified and no change is required, this will be recorded on Form 51.004D.

The requirement for any updates to the Risk Assessment will be discussed, agreed and documented at TMG meetings (Risk Assessment and Mitigations tracker are standing TMG Agenda items).

As per original Risk Assessment, Form 51.004D will be signed and dated by the SRC/SIC and CI to confirm either that new risks have been identified and mitigations recorded (Form 51.004E) or no new risks have been identified.

All signed Updates to Risk Assessment will be filed in chronological order alongside Version 1 of the Risk Assessment Tool in the TMF.

4. Referenced documents

- Form 51.004A - Risk Assessment Tool
- GUI 51.004A - Clinical Trial and Medical Device Risk Assessment Guidance Document
- Form 51.004D - Update to Risk Assessment Form
- Form 51.004E - Risk Assessment Mitigations Tracker
- Form 51.010E - R&I Study Strategic Plan
- SOP 51.016 - Preparation and Maintenance of a Trial Master File
- SOP 51.021- Review and Approval of Modifications for Research Sponsored by NHSGGC or Co-Sponsored by NHSGGC and the University of Glasgow
- SOP 56.001 Location Set Up Green for Go Process
- SOP 56.007 - Project Management Site Capability Assessment
- Form 56.007A – Site Capability Assessment Form
- Clinical trials for medicines: notifiable trials [Clinical trials for medicines: notifiable trials - GOV.UK](#)
- Medical Devices Regulations 2002 (as amended),
- ICH GCP E6 (R3) – Guideline for good clinical practice
- Clinical trials for medicines: guidance on quality and risk proportionality [Clinical trials for medicines: guidance on quality and risk proportionality - GOV.UK](#)
- Genetically Modified Organisms (Contained Use) Regulations 2014: [The Genetically Modified Organisms \(Contained Use\) Regulations 2014 - HSE](#)
- GMO (CU) Guidance Notes for Risk Assessment: <https://www.hse.gov.uk/biosafety/gmo/acgm/index.htm>

5. Related documents

- ECRIN risk assessment scale for risk adapted approaches to monitoring
- ICH Q9 Guidelines for Quality Risk Management
- Form 51.020B- Sponsor Oversight Checklist for Issuing RGL

6. Document History

Version	Date	Description	Retrospective Implementation
1.0	12/03/2013	Release of 1 st version	No
2.0	17/12/2015	Updated to template version 1.4. New risk assessment form template and process	No
3.0	05/05/2016	renumbered	No
4.0	24/05/2018	Hosted CTIMP risk assessment and clinical trial guidance document added.	No
5.0	18/01/2022	Updated from R&D to R&I and to include RA of non-CA marked medical devices, change of author	No
6.0	23/10/2026	Author changed, removed ref to Hosted CTIMP risk assessment. Inclusion of requirements in relation to GMO/FIH studies Updated RACI matrix, Added background, Updated references/links, Simplified text Removed non-CTIMP/Other research risk assessment process (a new SOP for this will be created) Updated to reflect new regulations Extensive changes throughout to include new process for risk assessment	No

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