SOP number	**53.010**	Version	**3.0**
Title	**Monitoring Clinical Research – Preparation and Management of a Monitoring Plan for a Clinical Trial of an Investigational Medicinal Product/Advanced Medicinal Investigation Product/ Medical Device Investigation/High Risk Non-CTIMP**		

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SOP category	NHS GGC Sponsor Governance

Staff category

Staff Category	**R**	**A**	**C**	**I**
Lead Clinical Trial Monitor		x		
Clinical Trial Monitors	x			
Research Governance Manager	x			
University of Glasgow Governance Manager				x
Chief Investigator			x	
Pharmacovigilance			x	
R&I Coordinator				x
R&I Lead Sponsor Pharmacist			x	
R&I Pharmacy			x	
Project Managers			x	
Statisticians			x	

1. Scope

This standard operating procedure applies to all NHS Greater Glasgow & Clyde (NHSGGC) Research & Innovation Clinical Trial Monitor(s) (CTM) and applicable to staff working within the Glasgow Clinical Trials Unit (GCTU). CTMs may monitor trials out with the NHS Greater Glasgow & Clyde Sponsor team, agreements with external Sponsors should be made in writing prior to the use of this SOP. (Please refer to SOP 53.014).

2. Purpose

The purpose of this SOP is to describe the procedures that will be used by the CTM acting on behalf of the Sponsor, either internal or external as per agreement to prepare a Monitoring Plan for clinical trials (CTIMPs, CIMDs and High Risk non-CTIMP) Sponsored by NHSGGC or hosted trials (commercial and non-commercial) when it is agreed, documented and resourced within a contract to perform this function by an external Sponsor. The trial monitoring NHSGGC will provide is dependent on the risks documented, within the protocol, risk assessment (SOP 51.004) and detailed, within the monitoring risk assessment (Form 53.010B) and documented in the monitoring plan (Form 53.010A) in compliance with the

trial protocol, the principles of Good Clinical Practice and the Medicines for Human Use Regulations
The Monitoring Plan will be updated throughout the course of the study as new risks emerge or change. This SOP describes the measures taken by the CTMs preparing the plan and will also describe the procedures for updating the Monitoring plan.

2.1 Resource

NHSGGC CTMs will provide a risk-based service dependent on the risks and available resources. However, the Monitoring team does not have the resource for the requirements of regulatory submissions and inspections for Marketing Authorisation, unless agreed prior to set up. Additional need for resource of the NHSGGC CTMs required for inspections and audits will be included within contracts and agreements, with the co-sponsor or owner of the IP liable for the risk and additional costs to NHSGGC.

3. Procedures

3.1. The Monitoring Risk Assessment

The type of monitoring included in the plan will be determined by a combination of the risk rating of the trial and other risks documented such as Phase of the trial, consent methods and key data such as safety and endpoints on Form 51.004A – Risk Assessment Tool, funding (and the overall monitoring risk score which is determined using Form 53.010B Monitoring Risk Assessment. The level of risk and how it is translated into the focus of monitoring objectives is described later.

Once the trial protocol has been approved or is close to approval and before the Sponsor green light approval happens the CTM will review the protocol and complete the NHSGGC Monitoring Risk Assessment (Form 53.010B) to determine the level and type of risks anticipated from a monitoring perspective. The monitoring plan is developed with a risk-based approach and will, therefore, take into account increased risks such as inadequate oversight, regulatory non-compliance for sponsor and trial risks to participant safety. Increased risks due to the complexity of the trial, the novelty of the interventions such as First In Human (FIH) Advanced Therapy Investigational Medicinal Products (ATIMPs) and Genetically Modified Organisms (GMO) studies, will ensure the monitoring is appropriate to the trial and is discussed below. The objective timelines, detailing the type and number of visits required and the rationale for these visits and timelines will be based on the risk of the study. The CTM will also consider risks in areas such as – location experience, training, deviations trends, IMP/GMO preparation/storage/delivery, associated trial tests/blood/samples/sample transfer etc. These will be covered in the monitoring risk assessments (Form 53.010B). In addition, the CTM will review the Sponsor Risk Assessment Tool (Form 51.004A) which is completed by the Research Coordinator, CI, Trial Team and Sponsor stakeholders at the start of any study, and determine if there are any issues which will impact monitoring. The Monitoring Risk Assessment (Form 53.010B) will be reviewed and approved by the Lead Clinical Trial Monitor/Research Governance Manager.

3.1.1 High Risk Studies

Some studies will have increased risks due to the complexity of the trial or the novel interventions, such examples are FIH, ATIMPs and GMOs. For all studies, the safety and wellbeing of trial participants must always be the priority and special consideration will be given to characterising risk and putting in place appropriate strategies to minimise risk. Depending on the study design, data generated throughout the trial in FIH/early phase trials may be used for decision processes for the ATIMP in regards to whether or not to dose escalate or not. (SOP 21.025) In order to make dose escalation decisions, key data will be source data verified at visits and documented on Form 53.010D. Visits to the research location may be high in frequency and extra visits may be needed to meet the objectives. In this type of study, trial specific reports are required from monitoring for decision making by the Safety Review Committee (SRC) where convened. The source data verification will be documented at each visit and sent to the SRC for review prior to decision of dose escalation.

The table below is an example of the output from Form 53.010B and outlines an example of scoring a risk assessment for a high risk study and how to mitigate the risks. Regardless of the perceived initial risk of any study, all questions will be answered in the NHSGGC Monitoring Risk Assessment (Form 53.010B). The example explores the risk encompassing the complex nature of the study design, primary and secondary endpoints, seriously ill or vulnerable population, inexperienced investigative location, a novel product and a high rate of missing data, transcription errors or protocol deviations. Areas of high risk or alert within the Monitoring risk assessment will be incorporated into the focus of the monitoring. Four categories including alert, high, medium and low risk are employed depending on the level of risk and score from, Form 53.010B.

The levels of risk are outlined below:

- Low Risk is defined as a score < 13
- Medium Risk is defined as a score of greater than >=13 but less than<= 26
- High Risk is defined as a score > 26
- Alerts are used for any high-risk studies for example GMO or FIH study.

N.B Any alerts will add 3 points on to the risk assessment score, these will be based on a study-by-study approach. Any alerts which will adjust SDV selection and monitoring schedule including number of visits will be stated specifically in the Monitoring Plan, (Form 53.010A).

Table 1: Example of a Risk Assessment (Qu.1 to 5)

Question	Indicator	Alert = 3	High = 2	Med = 1	Low = 0	Running Total	Risk Mitigation
1	Phase I/ First In Human (FIH) / GMO	3				3	100 per cent SDV monitoring. Time of first monitoring visit when first patient recruited. Consider any potential issues / dose escalation decisions/timelines. Consider reports for Safety Review Committee.
2	Study Design, complex study design with IMP dose escalation		2			5	100 per cent SDV monitoring. Time of first monitoring visit when first patient recruited.
3	Emergency Study with a number of different types of Consent		2			7	The monitor will risk assess the percentage of consents and aim to ensure these are reviewed in a timely fashion and give feedback to the location about their consents.
4	Novel Product (never used in humans before with dose escalation involved.)	3				10	First monitoring visit performed at first patient recruited. 100% SDV will be completed for dose escalation decisions and reports to the Safety Review Committee. The required data will be checked with the CI and the chair of the Safety Review Committee.
5	Primary and Secondary Endpoints captured at a specific timeline/visit			1		11	Focus SDV on these endpoints and ensure timelines are queried within eCRF.

(Full Risk Assessment must always be performed and documented)

3.2. The Monitoring Plan

The trial monitoring NHSGGC provide will be detailed within the risk assessment (SOP 51.004) monitoring risk assessment (Form 53.010B) and monitoring plan (SOP 53.010A). Based on both Risk Assessments, (Form 51.004A and Form 53.010B), and the definitions of the level of risk described in this form, the CTM will create a trial specific Monitoring Plan using the Monitoring Plan template (Form 53.010A).

The Monitoring Plan template (Form 53.010A) will document the risk score and risk classification detailing if it is high, medium or low risk study based on the monitoring risk assessment. It will set out the main risks identified in both the sponsor and monitoring risk assessments, (Form 51.004A and Form 53.010B), and how, if possible, to mitigate the risks. Strategic monitoring (i.e. central monitoring, on-site/remote must be documented in the Sponsor RA (SOP 51.004A) and the responsibility will lie with the co-sponsor/owner of the IP to ensure the risks are mitigated.

Key data will be agreed in collaboration with the CI and statistician then documented in the Sponsor Risk Assessment and the Monitoring plan (Form 51.004A and Form 53.010B). This data will be the focus for the CTM.

The visits may include but are not limited to; an initiation visit, a site compliance visit, full monitoring visit for both location and pharmacy, and site close out visit. The monitor will also consider any Laboratory or Imaging within the trial and whether or not it affects the primary endpoints of the study which may require an added objective to monitor or an extra visit. If laboratory endpoints, imaging or source data relate to exploratory outcomes, the monitor will document in the monitoring plan if these will be monitored depending on the risk in the Sponsor Risk Assessment (Form 51.004A). Each visit will be described within the plan detailing the objectives the monitor will aim to achieve based on trial specifications, assessment and mitigation of risks.

The monitoring plan will document the extent of central remote monitoring required, which may be due to costs or location circumstances. Central monitoring processes will be agreed between all relevant sponsor stakeholders and the responsible data centre prior to or early in the life of the study. This may include e-CRF report functionality and/or regular statistical reporting to provide oversight of safety and/or data quality issues. Any requests and responsibilities delegated to the data centre will be documented within the Sponsor RA (Form 51.004).

3.3. Review of the Monitoring Plan

Once the CTM has completed the Monitoring plan template (Form 53.010A), the plan will firstly be sent to the Lead Clinical Trial Monitor. The Lead Clinical Trial Monitor will review the monitoring plan to ensure risks relating to the trial activity have been incorporated and oversight and mitigation through monitoring planned for. The next step is to send the monitoring plan to the key stakeholders of the study including but not limited to, Project Manager, Sponsor Pharmacy, Research Governance Manager, Pharmacovigilance and the Chief Investigator for review. Key Data which affects primary or secondary objectives will be documented within the plan and reviewed by the Chief Investigator and the Statistician. The CTM will set a date for the Monitoring Plan (Form 53.010A) to be reviewed by and the date it was sent to stakeholders will be recorded on the document, any comments from the stakeholders addressed and incorporated with any relevant updates. If a stakeholder does not reply by the agreed review date, then the monitor will email the stakeholder a reminder giving them another five days to complete, if they do not reply after this date it will be

assumed the stakeholder has no comments to make on the plan and the plan will be finalised. The Project Manager will also document the review in the TMG minutes of the study. However, if any changes to the Monitoring plan are required on an urgent basis, the monitor must inform the TMG at the next available date that changes have happened with limited stakeholder review. After review by the key stakeholders, the Monitoring Plan will be reviewed and approved by the Lead Clinical Trial Monitor/Research Governance Manager. The final signed Monitoring Plan and Risk Assessment will be filed in the Monitors section of the Trial Master File. A copy of the final Monitoring Plan will be sent to the Chief Investigator (CI) for their information and site files.

3.4. Updating the Monitoring Risk Assessment and the Monitoring Plan

Over the course of the study, risks may change due to a protocol amendment, location compliance issues or other reasons. The Monitoring Plan and Risk Assessment must be updated and the monitor will complete the updated section of the Risk Assessment documenting the new risks. If monitoring findings indicate a review of the monitoring plan or risk assessment is required, this will be documented in the monitoring report in Q-Pulse. At every amendment the monitor must review the monitoring plan for any new risks and document via Form 53.010C. File Reviews are the responsibility of the designated CTM for the study, this should happen at least once over the lifetime of the trial, however, may be performed more frequently to ensure the monitoring risk assessment and monitoring plan are up to date.

3.5. Monitoring Plan Compliance

Compliance to the Monitoring plan will be reviewed monthly at the Monitors meeting and all CTMs will update the monitoring status of each of their allocated studies and ensure Status tracker columns relating to compliance to the monitoring plan have been completed. An example of these columns is highlighted in Appendix 1 of this document. It is the responsibility of the study CTM to ensure the monitoring plan is adhered to, ensuring the SDV has been performed and the relevant objectives have been achieved. A monitoring metrics report, produced by QA from the QMS, will be discussed at the meeting highlighting timelines for monitoring activity and reporting any non-compliances with location or pharmacy action, ensuring this has been escalated to the Governance Manager copying in the Sponsor Lead Pharmacist, as appropriate. Non-compliance will be documented and reviewed with the Lead Clinical Trial Monitor and/or Sponsor Governance Manager.

4. Referenced documents

- Form 53.010A - Monitoring Plan for a Clinical Trial of an Investigational Medicinal Product
- Form 53.010B - NHSGGC Monitoring Risk Assessment
- Form 53.010C - Research & Innovation Monitoring Plan Tracking Log
- Form 53.010D - Safety Review Committee Table
- Form 51.004A - Risk Assessment Tool.
- Form 51.016A - Sponsor TMF Index
- SOP 53.014 - External Sponsor Monitoring Arrangement
- SOP 50.020 - eCRF User Acceptance Testing (Glasgow Clinical Trials Unit)
- SOP 21.025 – Management of Dose Escalation In Early Phase IMP/ATIMP Clinical Trials

5. Related documents

- SOP 53.004 - Monitoring Clinical Research **–** Site Monitoring Visit
- SOP 56.001 - Location Set Up – Green for Go Process

6. Document History

Version	Date	Description	Retrospective Implementation
1.0	26/11/2020	First Release	No
2.0	18/06/2024	Significant updates to content, better reflect risk adaptation, oversight of compliance, review of amendments and change of Form numbers.	No
3.0	12/02/2026	Updated to ensure the process reflects the requirements of Sponsoring high risk studies, discussion of dose escalation and new safety review committee form.	No

Appendix 1.

Compliance Check - Monitoring Plan - Compliant Yes/No, add details as required	Compliance Check - Report timeline - Compliant Yes/No (as per SOP), please confirm if escalated	Compliance Check - Escalation follow up - Confirm if complete Yes/No