Research monitoring

PURPOSE

This work instruction identifies a consistent and enforceable process for research monitoring (including on-site and remote monitoring) for research being conducted within or in collaboration with Metro South Health (MSH).

OUTCOME

This work instruction aims to:

- Ensure that all MSH approved research is monitored in accordance with NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods. Monitoring of research refers to the process of verifying that the conduct of research conforms to the approved research protocol, is of the highest ethical and scientific standard, and is compliant with relevant legislation, standards, guidelines and the requirements of external regulators.
- Ensure that the monitoring of approved research is conducted in accordance with principles of compliance, accountability, transparency, quality control, risk management, health and safety, environmental protection and efficiency.
- Outline a consistent process to ensure the monitoring of approved research, that has been reviewed and approved by the Metro South Human Research Ethics Committee (MSHREC), is undertaken to assess that a research project is being or has been conducted in the manner approved by the MSHREC and in accordance with institutional requirements.

This work instruction outlines processes described in MSH procedure PR2023-413 Research administration and compliance and upholds principles outlined within the Research Administration and Compliance Handbook.

SCOPE

This work instruction applies to all MSH employees and collaborators who conduct human research within or in association with MSH, or through access to MSH participants, health records or data.

WORK INSTRUCTION

1. STEP 1: DEVELOP A MONITORING PLAN

- Monitoring Plans are developed and implemented by the Sponsor.
- Clinical trials which require a CTN notification, where MSH is the Sponsor in accordance with MSH work instruction WI2023-303 Metro South Health sponsorship of Clinical Trial Notification (CTN) scheme trials must have a Monitoring Plan as part of the research project documentation.
- A monitoring plan describes in detail the extent of the monitoring of a clinical trial and should:

- be tailored to the specific human participant protection and data integrity risks of the clinical trial.
- describe the strategy, methods, responsibilities, and requirements for monitoring the trial.

- Where MSH is the Sponsor, a Monitoring Plan Template will be developed collaboratively by the Coordinating Principal Investigator/Principal Investigator (PI/CPI) and Monitor, Metro South Research.
- The following templates can also be provided to the PI/CPI when required:
  - Preparing for a Monitoring Visit
  - Review of Investigator and Site Staff Suitability
  - Review of informed consent documentation
  - Review of compliance with the protocol and approved documents
  - Review of essential documentation
  - Review of source documents and the CRF
  - Review of investigational product management
  - Review of adverse event reporting documentation
  - Research sample/Laboratory Management Review
  - Monitoring Visit Report and Follow-up Activities
  - Remote Monitoring
  - Review of automated Statistical Monitoring reports
  - Close out monitoring visit activities
  - For-cause monitoring visits
  - Medicines Australia Collaborative Research Group – Clinical Trial Research Agreement
  - Study procedure Manual Outline (Template) – Single Centre
  - Study procedure Manual Outline (Template) – Multi Centre
  - Include Study Procedure Manual Template
  - Include Study Delegation Log Template.

1.1 Risk assessment

- The appropriate extent and nature of monitoring should be determined for a clinical trial based on considerations such as:
  - A risk assessment of the clinical trial intervention(s) relative to standard care and the extent of knowledge about the investigational medicines and/or devices being tested.
  - The complexity of the clinical trial protocol and supporting processes.
  - Factors such as objective, purpose, design, complexity, blinding, size and endpoints of the trial.
  - Experience of the research team.

- Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

- Refer to MSH work instruction WI2023-292 Assessing and managing risk in research for more information.

1.2 Monitoring plan template

- Where MSH is identified as Sponsor, a Monitoring Plan template will be provided by Metro South Research. This template includes the following components:
    - Description of the monitoring strategy, responsibilities of all the parties involved, the various methods to be used, and the rationale for their use.
    - Outline a systematic, prioritised, risk-based approach and emphasising the monitoring of critical data and processes.
        - Particular attention should be given to those aspects that are not routine clinical practice and that require additional training.
    - Identify the visit schedule and describe the types of visits to be conducted (i.e., interim monitoring visits, for-cause visits and close out visits).
    - In cases where the scope of monitoring permits, use varied approaches that improve the effectiveness and efficiency of monitoring (i.e. on-site monitoring only, a combination of on-site and centralised monitoring, or, where justified, centralised monitoring only).
    - Document the rationale for the chosen monitoring strategy in the monitoring plan.
    - Include reference the applicable MSH policies and procedures or project specific Standard Operating Procedures (SOPs).
- The monitoring plan should be documented and continually reviewed and adapted during the clinical trial, as real time assessments of safety data are performed.

1.3 Appointment of monitors

- The monitor(s) may be identified internally (from MSH) or externally to MSH.
    - External monitors are contracted to MSH for the purpose of monitoring, via engagement of a Contract Research Organisation (CRO).
    - Where an external monitor is used, they may be contracted to carry out all or a proportion of monitoring activities.
- Monitors should act with professionalism, honesty, integrity and maintain privacy at all times. Monitors must sign a confidentiality agreement with their employer (MSH or a CRO).

1.4 MSH-CRO agreement

- If a CRO is engaged to monitor a study, the MSH-CRO agreement must include a section outlining how confidentiality will be maintained by CRO employees involved in activities covered by the agreement at MSH and with MSH information.

1.5 Types of monitoring visits

- There are several types of study visits that may occur over the course of a study:

- site initiation visit
- interim monitoring visits (on-site or remote)
- for cause visits and
- close out visits.

- Refer to the Research Administration and Compliance Handbook attached to MSH procedure PR2023-413 Research administration and compliance for list of activities that may be conducted at the visits.

1.6 Interim monitoring visits – determination of the schedule

- The frequency of interim monitoring visits is dependent on the risks associated with the clinical trial. The risks may include trial phase, nature of the intervention, complexity of procedures and rate of participant recruitment.
- Metro South Research will refer to the risk assessment when determining the schedule for interim monitoring visits. The first interim monitoring visit should be scheduled as soon as possible after the first participant receives the intervention, and usually within 6-8 weeks of the intervention.
- Each site should have an on-site monitoring visit at least once per year during the active phase of the study. Monitoring should continue until the last participant has completed follow-up evaluations in accordance with the protocol.
- For multi-site visits, the monitoring schedule should be agreed to by the participating site and included in the monitoring plan along with clauses describing the responsibilities of all parties and associated procedures.

1.7 Budgeting for monitoring activities

- As part of the monitoring plan development process, the PI/CPI is strongly encouraged to include a budget for monitoring activities as part of:
    - the clinical trial budget; and
    - any funding applications/negotiations (i.e., grant applications, funding from companies etc).
- CPIs/PIs may also consider using monitors from a CRO however this may not always be feasible and other options may be investigated, including using internal MSH staff and directly contracting with experienced monitors.
- Refer to MSH procedure PR2023-413 Research administration and compliance for more information regarding research fees.

2. STEP 2: MONITORING PROCESS

2.1 Monitoring of single-site MSH investigator-initiated clinical trials

- Metro South Research is responsible for development and implementation of the clinical trial monitoring plan for single-site MSH initiated clinical trials. Monitoring may be performed by MSH staff or external contracted persons or entities acting under the supervision of the MSH PI.
- Refer to MSH procedure WI2023-303 Metro South Health sponsorship of Clinical Trial Notification (CTN) scheme trials for more information.

2.2 Monitoring of multi-site MSH investigator-Initiated clinical trials

- Where MSH is the Sponsor, the MSH PI must also act as the study CPI.
- Whether MSH acts as CTN Sponsor for non-MSH sites will be determined on a case-by-case basis in accordance with MSH procedure WI2023-303 Metro South Health sponsorship of Clinical Trial Notification (CTN) scheme trials.
- Each participating site must enter into an agreement with the lead site. The agreement should include the specific timing and duties concerned with monitoring and quality assurance, which are delegated to the sites according to the monitoring plan.
- The agreement must be executed prior to inclusion of trial participants at the site.
- Refer to MSH work instruction WI2023-302 Research contracts and study execution for more information.

3. STEP 3: ON-SITE MONITORING

- Monitoring of research may take various forms, including reports from researchers, review of safety reports, review reports from independent agencies, review of study site files, consent documentation, source documents and research data and on-site monitoring.

3.1 On-site monitoring activities

- During the on-site monitoring visit, the monitor should undertake activities outlined in the monitoring plan and in consideration of the clinical trial recruitment status.
- Refer to the Research Administration and Compliance Handbook attached to MSH procedure PR2023-413 Research administration and compliance for list of activities that may be conducted at the visits.

3.2 Scheduling an internal MSH on-site monitoring visit

- Metro South Research will contact a PI/CPI via telephone and in writing at least two (2) weeks in advance if their research project has been identified for an interim on-site monitoring visit.
- This notification will generally be by email and relevant templates will be provided to assist research team in preparation for the monitoring visit.
- Research on-site monitoring visits will vary from an hour to a full day. Metro South Research will assess how much time will be required and the on-site monitoring visit will be scheduled for a mutually convenient time.

3.3 Complete the monitoring self-assessment template

- The Monitoring Self-Assessment Template, provided at during the scheduling process, contains a list of specific information that will be reviewed on the day of the on-site monitoring visit. The PI/CPI and research team are encouraged to complete the template in preparation for the on-site monitoring visit.
    - Please also provide the signed Monitoring Plan to Metro South Research before the site initiation.

3.4 Non-response to an on-site monitoring visit request

- If a response is not received by Metro South Research within fourteen (14) days a reminder will be sent to the PI/CPI, nominated contact person and site head of department. Timeframes for response will be stipulated in the reminder notice. It is a requirement of ongoing HREC approval for monitoring to take place.

3.5 Final notification for an on-site monitoring visit request

- If there has been no response to the reminder request within fourteen (14) days then a final notification will be forwarded to PI/CPI, nominated contact person and site head of department. The notification will also be forwarded to the MSHREC Chair for their consideration/necessary action.

3.6 On-site monitoring visit

- The on-site monitoring visit will involve a meeting with the PI/CPI and research project personnel to discuss matters relating to the research and its conduct. At the commencement of the meeting a representative from Metro South Research Compliance will introduce the purpose of the on-site monitoring visit, ask general questions regarding the research project, note any relevant delegations and answer any questions regarding the on-site monitoring process.
- Following the introduction, the representative may request to see/review/verify the following in relation to the research project:
    - Trial Master File (TMF) and/or Investigator Site File (ISF) – contains specific/regulatory essential documents relevant to the research project. These are documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.
    - Source data including but not limited to:
        - Participant Information and Consent Forms (PICFs)
        - the process for obtaining informed consent
        - hospital charts and/or electronic records to verify eligibility
        - research project treatment and follow up as per research protocol
        - the reporting of serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR)
        - data storage and protection
        - investigational product storage and accountability (if applicable) and/or
        - the participant recruitment process.
    - For smaller research projects, the above will be assessed for every research project participant. For larger studies, Metro South Research will nominate a reasonable sample of research project participants for assessment. This sample will be randomly selected, but consideration may be given to assessing an equal number of participants from different treatment groups and/or including participants who did not complete the research protocol.

3.7 On-site monitoring findings

- During the on-site monitoring visit the representative from Metro South Research will discuss findings with the PI/CPI and research project personnel including recommendations and/or gaps in compliance. These may include:
    - regulatory requirements
    - employees and delegated responsibilities
    - research protocol and amendments
    - process for taking informed consent
    - research project participant recruitment processes
    - data and/or case report form recording
    - investigational product retention or accountability issues (if applicable) and/or
    - data protection.

3.8 Completion of monitoring

- Metro South Research will prepare a monitoring visit report and formal correspondence. On-site monitoring visit findings can be considered as major, moderate or minor. The on-site monitoring visit report will outline the findings of the on-site monitoring visit which will include a list of recommendations or actions to be completed. The formal letter and on-site monitoring visit report will be issued within two (2) weeks of the on-site monitoring visit.
- Copies of the on-site monitoring visit report and formal correspondence will be sent to the:
    - PI/CPI
    - research project coordinator and members of the research project team (as agreed with the PI/CPI)
    - relevant head of department (as appropriate)
    - MSHREC Chair and MSHREC Office for noting at the MSHREC meeting and Metro South Research Governance Office (MSRGO).
- A copy of the on-site monitoring visit report and formal correspondence will be filed in the HREC file. Metro South Research will retain all relevant documentation including correspondence and resolution of findings.

3.9 Follow-up actions

- It is the PI/CPI responsibility to ensure any necessary changes are implemented, however if any advice or assistance is required, Metro South Research will be available to help.
- The PI/CPI of the research project is obliged to respond to required actions within an agreed timeframe, generally a period of (3) three months or sooner. If issues are not resolved the matter will be referred to the MSHREC Chair and the MSRGO.

4. STEP 4: MAINTENANCE

4.1 Reviewing the monitoring plan

- The study monitoring plan should be reviewed and updated:

- in response to changes in risks of the study including identification of new risks and
- in response to outcomes of monitoring activities that identify deficiencies and where corrective/preventive action plans require more frequent monitoring.

- Changes in the clinical trial risk profile may arise from:
  - identification of risk that were not previously considered
  - evolving protocol - amendment to the protocol that affect the risk profile of the trial.
  - change in technologies, policies, legislation, or other requirements.
- The review of monitoring plans should be documented.

4.2 Annual report

- PI/CPI and research teams are required to submit a HREC/RGO Annual Progress/Final Report for each research project on **30 April** each year that the project is active.
- Annual reports must be provided to the MSHREC Office and MSRGO, in accordance with the MSHREC and SSA approval letters.
- Refer to MSH work instruction WI2023-306 Post approval – research amendments, reporting and closure for more information.

RESPONSIBILITIES

Position	Responsibility	Audit Criteria
Executive Management Team	• Ensure collaborative, harmonised, clear and detailed publicly available policies and procedures are in place for the ethical, scientific and Site Specific Assessment (SSA) review of research of all research conducted within MSH including monitoring.	N/A
MSHREC	• Review HREC/RGO Annual Progress Report/Final Reports for projects approved by the MSHREC and verify that research is being conducted according to the approved protocol and documentation, relevant contractual arrangements and regulatory approvals.	N/A
Metro South Research	• Ensure, via its SSA authorisation process, that all approved research is monitored in accordance with the National Statement, the Code and Good Clinical Practice (GCP). • Determine the frequency and type of monitoring undertaken which reflects the degree of risk to research participants and encompasses ongoing education of researchers in the responsible and ethical conduct of research.	N/A

	• Conduct monitoring audits on approved research.	
Monitor	• Responsible for acting under the direction of the sponsor. In the case of external monitors, the study monitor is responsible for acting: ○ under the direction of MSH if contracted directly to MSH or ○ under the direction of the CRO where a CRO is contracted to undertake monitoring activities.	N/A
Departmental directors/clinical trial coordinators	• Responsible for reviewing research projects within their departments however this is separate to the MSH monitoring process outlined in this work instruction.	N/A
Coordinating Principal Investigators (CPI)/Principal Investigators (PI) – responsible officer	• Fully co-operate with the on-site monitoring process and ensure that they respond to all queries and implement all necessary changes in the required time frame. • Ensure research practices reflect current professional (ethical and legal) standards for research, including promptly responding to reporting and monitoring requirements. • Ensure compliance with the approval given by a HREC, legislative and policy requirements for participant contact, consent and confidentiality of participant information. • Only conduct clinical intervention studies with the appropriate approved credentialing privileges and clinical experience. • Ensure that the delegated staff are appropriately trained and experienced to undertake study related tasks.	N/A
Study Coordinator and research team	• Researchers must comply with any requests from the sponsor in relation to monitoring. • The Study Coordinator or Contact Person nominated by the PI/CPI for the project at each site should be available during the Monitoring Visit to provide any documentation or answer questions as required.	N/A

DEFINITIONS

Term	Definition

Adverse drug reaction (ADR)	Adverse drug reactions concern noxious and unintended responses to a medicinal product.
Adverse event (AE)	Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to this medicinal product or not.
Clinical Trial *(National Clinical Trials Governance Framework definition)*	A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials include but are not limited to: • Surgical and medical treatments and procedures • Experimental drugs • Biological products • Medical devices • Health-related service changes • Health-related preventative strategies • Health-related educational interventions.
Collaborative Research Group Clinical Trials Research Agreement (CRG CTRA)	An agreement template that is to be used where a Hospital and Health Service (HHS) acts as and assumes all the responsibilities of a commercial sponsor.
Contract Research Organisation (CRO)	A company that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.
Good Clinical Practice (GCP)	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.
Investigator-initiated trial	A clinical trial that has the following characteristics: • A pharmaceutical/device company is not acting as the sponsor for the purposes of the CTN application. • A pharmaceutical/device company is not fully funding the conduct of the study, that is, making payment to the relevant hospital or investigator. • The clinical trial addresses relevant clinical questions and not industry needs. The PI/CPI or the Hospital/Institution is the primary author and custodian of the clinical trial protocol.

Research Monitoring	ICH GCP defines monitoring as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).
Principal Investigator (PI)/Coordinating Principal Investigator (CPI)	An individual responsible for the conduct of a clinical trial at a trial site ensuring that it complies with GCP guidelines. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the CPI/PI In this instance they may delegate tasks to other team members.
Serious adverse event (SAE)	Any untoward medical occurrence that at any dose: • results in death • is life-threatening (NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe). • Requires inpatient hospitalisation or results in prolongation of existing hospitalisation. • Results in persistent or significant disability/incapacity. • Is a congenital anomaly/birth defect. • Is a medically important event or reaction.
Sponsor	An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial'. Note the term Sponsor is relevant to all research – not just commercially sponsored research (e.g., grant-funded, or unfunded research may be sponsored by the university or hospital that is the administering institution).
Ethical Review Manager (ERM)	Web based content manager supported by the Office of the Director General via Office of Research Innovation, Queensland Health.

RELATED AND SUPPORTING DOCUMENTS

Legislation and other Authority	**Legislation (as updated and replaced from time to time)** • *Australian Research Council Act 2001* (Cth) • *Hospital and Health Boards Act 2011* (Qld) • *Financial Accountability Act 2009* (Qld) • *National Health and Medical Research Council Act 1992* (Cth) • *Public Health Act 2005* (Qld) • *Public Sector Ethics Act 1994* (Qld)

	• *Research Involving Human Embryos Act 2002* (Cth) • *Therapeutic Goods Act 1989* (Cth) **Regulations** • *Financial Accountability Regulation 2009* (Qld) • *Financial and Performance Management Standard 2009* (Qld) • *Hospital and Health Boards Regulation 2012* (Qld) • *Public Health Regulation 2018* (Qld) • *Therapeutic Goods (Medical Devices) Regulations 2002* (Cth) • *Therapeutic Goods Regulations 1990* (Cth) **Other authority** • National Statement on Ethical Conduct in Human Research (2023) • Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) • ICH Quality Guidelines • ISO 9001:2015 Quality management systems - Requirements **Department of Health** • Health Service Directive: Research Ethics and Governance Directive QH-HSD-035:2023 • Research Management Policy QH-POL-013:2022 • Research Management Standard QH-IMP-013:1:2022 **Metro South Health** • Metro South Health Research Strategy

Standards	• National Clinical Trials Governance Framework
	• National Safety and Quality Health Service (NSQHS) Standards 2nd Ed.
	  ○ Standard 1 – Clinical Governance
	  ○ Standard 2 – Partnering with Consumers

Supporting documents	**Procedures** • PR2023-411 Research excellence • PR2023-412 Research support and management • PR2023-413 Research administration and compliance **Work instructions** • WI2023-299 Ethical and scientific review of research • WI2023-300 Exemptions from research review • WI2023-301 Site specific assessment in research • WI2023-302 Research contracts and study execution

	• WI2023-303 Metro South Health sponsorship of Clinical Trial Notification (CTN) scheme trials • WI2023-304 PowerTrials - ieMR research support module • WI2023-306 Post approval – research amendments, reporting and closure **Guidelines** • GL2023-99 Planning a research project • GL2023-100 Research Participant Information and Consent Form (PICF) • GL2023-101 Research contract clauses • GL2023-102 Use of electronic signatures in research contracts • GL2021-77 Clinical trials • GL2023-103 TeleTrials

HUMAN RIGHTS ACT 2019

Metro South Hospital and Health Service is committed to respecting, protecting and promoting human rights. Under the *Human Rights Act 2019*, Metro South Health has an obligation to act and make decisions in a way that is compatible with human rights and, when deciding, to give proper consideration to human rights. When deciding about research, decision-makers must comply with that obligation. Further information about the *Human Rights Act 2019* is available at: https://www.forgov.qld.gov.au/humanrights.

WORK INSTRUCTION DETAILS

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Version	Approval date	Effective from	Authority	Comment
1.0	7/12/2023	13/12/2023	Chief People, Engagement and Research Officer	• Supersedes PR2017/117 Monitoring Procedure