Research quality management systems

PURPOSE

This work instruction identifies an effective process to establish quality management systems which aims to improve the quality and impact of research being conducted within or in collaboration with Metro South Health (MSH).

OUTCOME

This work instruction aims to:

- Ensure all research conducted within MSH or in collaboration with external entities, is of the highest quality and in compliance with the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6 (R2) (2016) ('GCP Guideline').
- Outline a MSH-wide process that can be adapted by MSH research teams to implement quality management systems and processes for their research projects.

This work instruction outlines processes described in MSH procedure PR2023-411 Research excellence and upholds principles outlined within the Research Excellence 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: PLAN - IDENTIFY QUALITY OBJECTIVES, RISKS TO QUALITY AND METRICS

1.1 Research protocol design

- Principal Investigator (PI) must ensure that consideration is given to quality and reporting requirements when developing research protocols for research projects. For high quality research, participant safety and data accuracy must be safeguarded by ensuring:
    - that appropriate information is provided to participants (consent)
    - safe administration of investigational products and monitoring of potential Adverse Events (AE)
    - safe study procedures and investigations which enhance public health and safety more broadly
    - appropriate data collection, management and reporting throughout the study.
- The research protocol must be written in a way that if the PI is unable to complete the project, another suitably researcher can pick up and continue the work. MSH guideline GL2023-99 Planning a research project provides further information.

1.2 Risk assessment and management

- As part of this process, it is important to:
    - Assess risks – likelihood and impact across the life of the research project.
    - Plan mitigation – how those risks will be managed proactively to help minimise their likelihood and impact.
    - Plan evaluation – how will actions be monitored to ensure strategies are working.
- MSH work instruction WI2023-292 Assessing and managing risk in research provides further guidance.

1.3 Feasibility

- Research feasibility typically encompasses checking various aspects to ensure the successful execution of the proposed research project. Table 1 below provides some key feasibility check examples:

Table 1: Examples of key feasibility checks	
Expertise and workload	The qualifications, experience and the workload of the PI and the research staff needs to align with the needs of the research project.
Regulatory compliance and approvals	The time and effort required to submit and obtain necessary regulatory approvals in a timely manner needs to be considered.
Budget and financial considerations	A thorough budget allocation needs to be developed to include all site fees, personnel costs, and other study-related expenses to ensure adequate funding throughout the study. Potential cost saving strategies should not compromise the research quality and integrity.
Data management	The methods and the capacity to collect, record, manage and report accurate and complete research data as per GCP guidelines need to be considered.
Participant recruitment and retention	Possibility of recruiting and retaining sufficient number of eligible participants within specified timelines needs to be assessed considering disease prevalence, patient demographics and recruitment strategies.
Logistical considerations	The availability of necessary facilities, equipment and resources needs to be reviewed including imaging or laboratory services and storage of investigational product and/or biological specimens. Transportation logistics of the investigational product and/or the biological specimens also needs consideration where applicable.

1.4 Quality by design – ensuring participant/patient safety and data accuracy

- Quality by design is a systematic approach to drug and device development. The principles of quality by design should be adhered to when planning/undertaking a research project:
    - **Pre-defined objectives**: A scientifically sound protocol and data management plan.

    - **Emphasises process understanding**: Defined processes including Standard Operating Procedures (SOPs), training plans etc.
    - **Controls the process based on sound science and quality risk management**: Monitoring processes and risk management strategies.
- Quality by design assists in avoiding errors, collects data that is fit-for-purpose, reduces patient burden and focuses resources on the reliability of data and patient safety during a research project. Refer to the following attachments that are useful to develop high quality research protocols and related documents:
    - Research protocol templates (attached to MSH guideline GL2023-99 Planning a research project)
    - Attachment 1: SOP template
    - Attachment 2: Site file index template
    - Attachment 3: AE log
    - Attachment 4: SAE report form
    - CV Template (Transcelerate)
    - Delegation Log (Transcelerate)

1.5 Recording Adverse Events (AEs) and reporting Serious Adverse Events (SAEs)

- Recording AEs and reporting SAEs in a timely manner are of paramount importance as they play crucial role in ensuring participant safety, maintaining data integrity and upholding the ethical standards of research.
- Accurate data collection and documentation safeguard against bias, error and misinterpretation. The commitment to data accuracy ensures that the outcomes of a study truthfully reflect the effects of the study intervention and the research setting. Misreported or inaccurately recorded data can distort findings leading to misguided conclusions that can impact patient care, regulatory decisions and the future research directions.
- For **research related incidents**, for example, protocol violations that **do not** impact upon patient safety, only require reporting to the approving Human Research Excellence Committee (HREC).
- For **research clinical incidents**, the matter must be addressed within the clinical team and reported by MSH's Clinical Incident Reporting System (RiskMan) as well as to the approving HREC.
- MSH research clinical incidence reporting structures are outlined in MSH procedure PR2023-412 Research support and management.

1.6 Standard Operating Procedures (SOPs)

- The key purpose and role of research SOPs is to help the project team, unit or institution remain compliant with Good Clinical Practice (GCP). Since research is global, the GCP Guideline standards recognise the importance of standardising methods of performing, analysing and regulating clinical trials across nations. SOPs are an effective way of supporting this aim.

- The GCP Guidelines mention SOPs as a way to implement quality processes that protect the safety and welfare of human participants. SOPs are a fundamental part of research quality management system and should form part of any research project.
- SOPs in research should contain adequate detail, have a general and consistent format and style, be distributed through education and training, reference applicable guidelines, contain definitions and abbreviations, include department authorisation and contain review and monitoring requirements.
- See the National Standard Operating Procedures for Clinical Trials, including Teletrials, in Australia for more information and examples of common SOPs in research projects.

1.7 Version control

- SOPs must have version control and update history and all other SOP requirements.
- Version control is a system that enables reviewers to manage changes to a document and track different versions of those documents overtime. While the specific implementation of version control systems may vary, the underlying principles remain consistent.
- Version control should be used where more than one version of a document exists, or where this is likely to be the case in the future.
- Version control can be achieved by adding a number at the end of a file title. Each successive draft of a document is numbered sequentially from 0.1, 0.2, 0.3… until a finalised version is complete. This would be titled version 1.0.
    - Example: The first version number of a document is saved as v0.1 and the watermark 'Draft' added. As the document is reviewed and revised the file's naming convention number increments by 1 to become v0.2, v0.3, v0.4 etc. Once the final revision has been approved and is able to be distributed/implemented it becomes a v1.0 document and the 'Draft' watermark is removed. Only documents with a v1.0, v2.0, v3.0 etc. are considered final and able to be distributed published.
        - Initial revision of document by author saved as: 230501_Research_Guide_PICF_v0.1
        - Revision of document by Principal Investigator saved as: 230502_Research_Guide_PICF_v0.2
- If version 1.0 is to be revised, drafts would be numbered as 1.1, 1.2, etc. until version 2.0 is complete.
- To keep versions organised, a dedicated folder for the document should be created and all the revisions and versions saved inside it. This enables a clear overview of the document's history and easy access to specific versions when needed.
- As stated above, the MSHREC and Research Governance Office (RGO) require copies of tracked changes and clean versions. Below is an example of how these revisions can be saved in the file:
- Example:
    - 230531_Research_Guide_PICF_v2.2_Tracked
    - 230531_Research_Guide_PICF_v2.2_Clean
- Once the above document is approved, finalised and able to be distributed it becomes a v3.0 version:
- Example:

- 230531_Research_Guide_PICF_v3.0

- In addition to adding the version number to the end of the file title, it should also be displayed within the document. The version number should appear on any document title page, and also in the header or footer of each page.

2. STEP 2: DO - CONDUCT RESEARCH PROJECT

2.1 Quality management frameworks

- Implement appropriate quality management frameworks that:
    - maintain participant confidentiality and complies with ethical review requirements. MSH work instruction WI2023-299 Ethical and scientific review of research provides more information.
    - establish quality provisions which must also comply with the National Statement on Ethical Conduct in Human Research (2023) ('National Statement').
    - reduce the likelihood of random errors which may impact upon the accuracy of data and system errors which are identified causes that result in incorrect data.
    - comply with MSH work instruction WI2023-289 Research data and privacy the collection and use of data.

2.2 Conduct of research

- Researchers must ensure research is conducted in accordance with the Research Policy Framework. Researchers must also:
    - maintain the reliability of data by ensuring that the data collected and reported on from each research project is accurate, and will detect ‘true effects’ from clinical interventions – new drugs and devices; and
    - ensure that the findings make a valid contribution (positive or negative) to the existing body of knowledge.
- When conducting the research, it is important to maintain:
    - Organisation: does the project have the right resources, equipment and agreements in place
    - Training: are all staff and other collaborators appropriately training in general terms plus study specific items
    - Systems and procedures tailored to the protocol: are SOPs and other policies appropriately aligned to the research project.

2.3 Quality management system

- Researchers should implement a quality management system which manages all the documents, activities, tasks, processes, quality events, relationships, audits and training that must be controlled throughout the life of a research project.
- It is based on the principles of quality management used across many industries as articulated in ISO 9001:2015 and ICH 56, E9 and Q10 – Good Manufacturing Processes.

- A risk register forms part of the system and should be implemented for each research project. MSH work instruction WI2023-292 Assessing and managing risk in research provides further information.

3. STEP 3: CHECK COMPLIANCE - MEASURE AND MONITOR

3.1: Monitoring

- The Principal Investigator has primary responsibility for ensuring research is appropriately monitored and that all members of the research team are appropriately supervised.
- Researchers also have a responsibility to continuously:
    - Monitor and evaluate performance: does the research project have a system for prospectively and retrospectively assessing and evaluating activities
    - Monitoring: how will the research project be monitored, what action and activities are in place to ensure the team is mitigating or managing risks.
- Research projects are also monitored in accordance with MSH work instruction WI2023-305 Research monitoring.

3.2 Reporting and third-party engagement

- Researchers are responsible for ensuring that the HREC/RGO Annual Progress Report/Final Report is submitted prior to the MSHREC clearance anniversary (or sooner as required), to comply with MSHREC clearance requirements.
- MSH work instruction WI2023-306 Post approval – research amendments, reporting and closure provides further information.

4. STEP 4: ACT - RESPOND TO DEVIATION

4.1 Action

- Should a deviation be identified that impacts upon the participant's safety and the reliability of data, the research team must act immediately to rectify. The research team should:
    - implement corrective and preventative action (CAPA) to identify, address and prevent issues and non-conformities.
    - re-assess risks by routinely looking at identified areas of risk and making sure they are unchanged or new threats are addressed.
    - make appropriate changes/amendments to protocol, operations or monitoring. There needs to be a process for changing/amending the research project that is open and transparent to all staff and stakeholder.
- MSH work instruction WI2023-306 Post approval – research amendments, reporting and closure provides further information.

RESPONSIBILITIES

Position	Responsibility	Audit criteria
Executive Management Team	• Responsible for providing advice and oversight of MSH procedures relating to research and innovation (including research conduct), commercialisation and research higher degree training (including issues of quality). • Responsible for implementation of the research policies and procedures and for fostering good research practices.	N/A
Metro South Research	• Provision of information resources and services pertaining to research to MSH and oversight of research development in MSH. • Leadership for embedding a culture of responsible research conduct. • Ensuring the administrative processes for ethical approval and SSA authorisation of all human research are in place and promotes research integrity. • Assessing the adequacy and effectiveness of MSH's internal controls, including the risk management and compliance frameworks. • To manage risk to patients/participants and employees as well as financial and reputational risk.	N/A
Principal Investigator (PI)/ Coordinating Principal Investigator (CPI) - responsible officer	• Ensure quality is considered when developing research protocols and processes are in compliance with the Research Policy Framework. • Manage quality throughout the stages of a research project process/lifecycle. • Ensure the safety and wellbeing of participants and the reliability of data.	N/A
Employees, researchers, research student supervisors and students	• Share responsibility and accountability for MSH's research being conducted according to appropriate regulatory, ethical and scientific standards.	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.
Correction and Preventative Action (CAPA)	CAPA is a method used to identify a discrepancy/problem in the conduct of a research study, note the root cause of the identified problem, identify the corrective action to prevent the recurrence of the problem, and document that the corrective action has resolved the problem.
Ethical Review Manager (ERM)	Web based content manager supported by the Office of the Director General via Office of Research Innovation, Queensland Health.
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.
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.
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).
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).
Standard Operating Procedures (SOPs)	SOPs are uniformly written procedures, with detailed instructions to record routine operations, processes and practices followed within a business organisation. In clinical research, SOPs help define standard practices, procedures and daily processes conducted to assure execution of research tasks in accordance with institutional, state and federal guidance's - "ICH GCP E6 (R2) 1.55 Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of a specific function.
Version control	Version control is the process by which different drafts and versions of a document or record are managed. It is a tool which tracks a series of draft documents, culminating in a final version. It provides an audit trail for the revision and update of these finalised versions.

RELATED AND SUPPORTING DOCUMENTS

Legislation and other Authority	**Legislation (as updated and replaced from time to time)** • *Hospital and Health Boards Act 2011* (Qld) • *National Health and Medical Research Council Act 1992* (Cth) • *Public Health Act 2005* (Qld)

	• *Public Sector Ethics Act 1994* (Qld) • *Therapeutic Goods Act 1989* (Cth) **Regulations** • 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 • Finance Management Practice Manual (FMPM) • Human Resources (HR) Delegations Matrix and Schedule • Metro South Financial Delegation Schedule and Framework • MSH Risk Management Framework • MSH Risk Assessment Tool • MSH Risk Appetite Statement • Risk Register - CAMMS • CAMMS Data Definitions

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 • WI2023-287 Research integrity • WI2023-289 Research data and privacy • WI2023-290 Research authorship, peer review and publication • WI2023-291 Research complaints and misconduct • WI2023-292 Assessing and managing risk in research **Guidelines** • GL2021-75 Research Management - Partnering with Consumers in Research • GL2023-97 Aboriginal and Torres Strait Islander health research • GL2023-98 Research translation and impact **Attachments** • Attachment 1: SOP template • Attachment 2: Site file index template • Attachment 3: AE log • Attachment 4: SAE report form

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 making a decision, to give proper consideration to human rights. When making a decision 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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