Standard Operating Procedure

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Document History

Revision	Modified by	Date of Release	Description of Change
1.0	Jenny Munro & Dianne Tucker	1/08/2024	New Issue

Contents

1. PURPOSE

This SOP describes the internal audit procedures of the RCH Research Ethics and Governance Office (REG) and Melbourne Children's Trial Centre's (MCTC's) Quality Assurance (QA) team. The REG office conducts internal audits on behalf of RCH and MCTC conducts internal audits on behalf of MCRI.

1.1 Quality Improvement

This SOP provides the procedure for RCH REG and MCTC's Quality Assurance team to conduct internal audits of research projects, as part of the Melbourne Children's Clinical Research Governance Framework. The internal auditing program contributes to the ongoing institutional oversight of human participant research. A major component of this is oversight of data quality and safety (see 1.2) of participants of research.

Internal auditing identifies non-compliance with standards and regulations designed to generate high quality data. It also provides an avenue to implement corrective and preventive action (CAPA) plans to mitigate/reduce the impact of non-compliance.

1.2 Participant Safety

Auditing may identify issues with management of safety monitoring and reporting. In this case the internal auditor will identify actions for the research team and follow up on the implementation of any actions/CAPAs.

2. BACKGROUND

Internal auditing is an assessment of compliance with defined standards at a given moment in time. Internal auditing is distinct from 'monitoring' which refers to the research team's continuing research oversight and quality control measures.

National and international guidelines outline the role and responsibilities of both Research Institutions and Clinical Trial Sponsors for auditing human participant research projects.

As such, it is necessary to undertake internal audits of research practices to assess compliance to the study protocol, GCP, SOPs, and all applicable legal and regulatory requirements as a part of a quality management system.

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The purpose of a research internal audit is to:

- evaluate trial conduct and ensure researchers' compliance with the protocol, SOPs, GCP, regulatory requirements and MCC policy
- ensure participant and staff safety
- ensure participant rights, welfare and well-being are being adequately protected.

- assess data quality and integrity
- improve research systems and data quality
- prepare researchers for external audit processes
- demonstrate robust research processes to external funders and industry.

Research projects may be subject to an internal audit for a variety of reasons either planned or 'for cause' such as:

- HREC request following approval of a new protocol as part of the approval process
- risk classification
- random selection
- complaint
- annual report verification

3. SCOPE

This SOP describes the processes used by both the RCH Research Ethics and Governance Office (REG) and Melbourne Children's Trial Centre's (MCTC's) Quality Assurance Team as internal auditors for:

- selecting studies for internal audit.
- conducting internal audits
- reporting internal audit results to the auditee
- reporting to the relevant institutional governing bodies
- CAPA implementation and monitoring
- following up action completion

It describes the responsibilities and actions for the auditees/delegates during an internal audit.

The procedures outlined in this SOP are not limited to clinical trials but also include observational studies, clinical audit activities and public health research projects.

The scope of the REG and MCTC internal audits includes reviewing project documentation for compliance with applicable MCC policies, SOPs, legislation, regulations and guidelines. This may include:

- ICH GCP (current version adopted by TGA/external regulatory body (as applicable)
- NHMRC National Statement on Ethical Conduct in Human Research (2023)
- NHMRC Australian Code for the Responsible Conduct of Research (2018)
- MCC Clinical Research Governance and Support Handbook
- Research Policy – Responsible Conduct of Research at Melbourne Children's

3.1 Out of Scope - Monitoring

Monitoring is an ongoing activity throughout the conduct of a research study. Refer to MCTC046 SOP Monitoring Visit Activities for Clinical Trials of Investigational Products.

4. RESPONSIBILITY

The RCH REG, on behalf of RCH, and Melbourne Children's Trial Centre's (MCTC's) Quality Assurance team, on behalf of MCRI, have partnered to share the internal auditing function for Melbourne Children's Campus (MCC).

RCH REG has overall responsibility for all clinical research projects authorised by the HREC including clinical trials, observational studies, clinical audit activities and public health research projects.

MCTC's Quality Assurance team will conduct internal audits of MCRI-sponsored investigator-initiated trials.

4.1 Internal Audit Schedule

The RCH REG Office team in collaboration with the MCTC are responsible for establishing the annual internal audit schedule.

The schedule is informed by recommendations from the HREC (e.g. high-risk projects, identified risks and consumer feedback) and the MCRI Sponsorship Committee.

The schedule will include a mix of 'horizontal audits' based on thematic risks (e.g. waiver of consent, opt-out) and 'vertical audits' (deep dive audits) based on suggestions or 'for cause' from relevant committees (refer to the Risk Factors for Study Selection table in 5.2.2 Sampling Selection).

The annual internal audit schedule will be drafted and presented to the Melbourne Children's Clinical Trial Governance Committee for endorsement.

4.2 Role of the Internal Auditor

Lead Internal Auditors take the leading position within an internal audit team and supervise the 'internal auditors' through the internal audit process.

The table below shows a 'high level' summary of the roles and responsibilities of Lead Internal Auditors and Internal Auditors. Further details are included in the Lead Internal Auditor and Internal Auditor training modules.

Function	Lead Internal Auditor	Internal Auditor
Selection Selects the internal auditors, assigns roles within the team, identifies what to audit.	✓	
Internal Audit Schedule Determines number and types of internal audits to be conducted, develops internal audit schedule, seeks endorsement of internal audit schedule, assigns internal auditors to conduct audits.	✓	
Conducting the Internal Audit Communicates internal audit with auditee, conducts the 'field work' for the internal audit.	✓	✓
Reporting Results The internal auditor writes a report at the conclusion of the internal audit and assigns corrective and preventive actions with oversight of the Lead Internal Auditor.	✓	✓
Follow-Up Corrective Actions Ensure any non-conformances have a corrective and preventive action plan (CAPA); monitor completion of the CAPA; share themes	✓	✓
Closing the Internal Audit Ensure all CAPA have been completed with objective evidence. :	✓	✓

*Green tick indicates primary responsibility

Black tick indicates it can be involved but is not a primary responsibility

4.3 Role of the Auditee

It is the role of the auditee and study team delegates to be available for an internal audit visit at the agreed time and location and to provide all information as requested by the internal auditor. The internal audit may be conducted in person or via remote access. The auditee will also be required to respond to findings, collaborate on a CAPA plan, rectify identified issues and undertake report recommendations.

5. PROCEDURE

5.1 Internal Auditor Qualification

Internal auditors must be independent of studies being audited and qualified by training and experience.

Lead Internal Auditors are to be suitably qualified by undertaking a training module 'Lead Internal Auditor Training' (or as part of a Quality Management course). These Lead Internal Auditors can then use a 'train the trainer' model to educate Internal Auditors. Internal Auditors will work under the supervision of the Lead Internal Auditor.

5.2 Selection Process

5.2.1 Types of Internal Audits

Appropriate levels of internal auditing and assessment will occur dependent on the study type and level of risk the research study poses to the institution, research staff and research participants.

Internal audits may be one of two types:

a) Horizontal audit: involves tracking a particular process across many research studies. For example, a specific topic such as 'consent' may be audited across all or a number of studies.
b) Vertical audits: involves assessing all processes and activities undertaken in a single study.

5.2.2 Sampling Selection

Studies will be selected based on the risk factors listed within the table below. The Lead Internal Auditors are responsible for selecting the studies for internal audit. The Lead Internal Auditors will seek input from the Human Research and Ethics Committee and MCRI Sponsorship Committee.

Example risk factors for study selection
• Study population (e.g. size, vulnerable subjects, new indications) • Product characteristics (e.g. new products or with specific risks) • Therapeutic area • Duration of study • Applicability of regulations (e.g. international vs non-international) • Importance of study to future marketing submission (e.g. study phase, pivotal or supporting study) • Level of experience of research/clinical team • Confidence in service providers • Number and nature of outsourcing activities and associated interfaces for responsibility • Level of complexity of study and training requirements (e.g. e-system usage/medical device requirements) • Regional distribution of sites

The decision to conduct a 'for cause' internal audit will be on a case-by-case basis and the below would be discussed at the RCH Research Operations monthly manager's

meeting. Recommendations may also come from the MCRI Sponsorship Committee or the Human Research and Ethics Committee.

Example of 'for cause' study selection
• Serious breach • Regulator directed • Whistle blowing • Lack of correct study approvals in place • Temporary halt • Inadequate data entry • SAE misreporting • Critical finding at monitoring visit • System non-compliance • Multiple protocol deviations that lead to subject safety or data integrity of a study

5.3 Internal Audit Plan

An internal audit plan specific to the selected study will be developed by the Lead Internal Auditor/s and sent to the auditee or delegated individual involved prior to beginning the internal audit.

The plan will:

- provide rationale for internal audit
- define scope and objectives for internal audit
- provide timelines for internal audit to be conducted
- identify where and when the internal audit will take place
- identify requirements to be audited against
- identify groups and areas to be audited
- list documents and records to be reviewed
- list responsible people whose functions will be audited
- specify who will receive the final report

The auditee or delegate ensures that the internal auditor will have access to:

- study files and documents, including electronic versions
- list of participants
- signed consent form for every participant enrolled in the study
- participant data files, including medical records*, for the nominated research participants specified in the initial letter

- a member of the research team to answer any questions
- a space for the monitor to sit and review the documents
- database** containing the study data

*If medical records need to be requested from Health Information Services with advanced notice, the researchers must account for this to make sure the correct and complete records are available.

**A researcher with authorised access who is familiar with the database is required to assist the internal auditor on the database.

5.4 Internal Audit Visit

The time commitment for the internal audit visits will vary depending on the complexity of the study, whether the internal audit visit is conducted in person or via remote access.

The auditee needs to be available to answer questions for at least 30 minutes at the start, during (as required), and 30 minutes at the end of the visit.

The process will start with an opening meeting where the Lead Internal Auditor / Internal Auditor explains the scope and objectives of the internal audit, and how the internal audit will be conducted.

Internal audit activities will include:

- interviewing researchers and support staff
- visit to laboratory/pharmacy (site internal audits only, and if applicable)
- reviewing documents and systems
- observing activity, e.g. informed consent
- documenting observations

The documents/systems reviewed during internal audit will vary depending on the scope of the internal audit and if the research is led by MCRI (and therefore MCRI-sponsored) or led by an external sponsor.

Documents/systems reviewed for MCRI-sponsored research may include (but not be limited to):

- Study/Trial Master File, including:
    - Study approvals/authorisations including ethics, CTN, international regulators (as applicable)
    - Study protocol
    - Reports to HREC, Site Principal Investigators, TGA & international regulatory bodies (If applicable)
    - Training and delegation logs
    - Training of site teams
    - Site Information Files
    - Communication within the central coordinating team and participating sites

    - Manual of Procedures / Study-specific SOPs
    - Data Management Plan, Clinical Monitoring Plan
    - Monitoring Visit Reports
    - Adverse event listing
    - Central non-compliance (serious breaches) log
    - Corrective & Preventive Action Plans (CAPAs)
- Study database and other computerised systems
    - Validation records

Documents/systems reviewed for externally sponsored studies may include (but not be limited to):

- Investigator Site File, including
    - Study approval/authorisations including ethics, local governance, CTN (as applicable)
    - Communications with Sponsor, Research Ethics & Governance Office, Supporting Departments
    - Study protocol
    - Training and delegation logs
    - Participant source data, including EMR, signed participant informed consent forms
    - Case Report Form (CRF) – if electronic CRFs have been used, the internal auditor will need read-only access set up
    - Study medication dispensing records, equipment maintenance/calibration records
    - Non-compliance (serious breaches) log
    - Corrective & Preventive Action Plans (CAPAs)

5.5 Audit Findings and Report

The internal audit report will include:

- areas of excellence
- breaches of the conditions of HREC approval
- non-compliance with the protocol
- non-compliance with the Investigators Responsibilities in Research and Informed Consent in Research procedures
- non-compliance with relevant Melbourne Children's Standard Operating Procedures

Non-Compliances are graded according to the table below:

Critical:	A finding defined as one with the capacity to directly undermine the integrity of the entire study. It's a weakness of, or non-compliance with, one or more processes indicating a systematic quality assurance failure which, if not resolved, will cause

	harm to patients or data integrity and/or organisation reputation that requires the **immediate notification** and attention of senior management and clear timelines for resolution. Critical finding examples: • Where evidence exists that the safety, wellbeing, rights or confidentiality of study participants has been (or has had significant potential to be) jeopardised. • Where reason has been found to cast serious doubt upon the accuracy and/or credibility of study data. • Where approval for the study has not been sought from one or more regulatory agency/body or granted from one or more regulatory agency/body (e.g. Ethics committee, Site governance) but the study has commenced regardless. • Where significant procedures not covered/included on the consent form are being performed or where new procedures have been introduced into the study protocol but where participants who had consented prior to their introduction have not been asked to re-consent. • Where following study approval, significant amendments have been made to the study protocol or documentation but no new request for approval has been submitted. • Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported major findings. A combination of multiple “major” audit findings may result in a “critical” systemic audit finding even though each of the findings is not “critical”.
Major:	A finding defined as one that compromises the integrity of a certain component(s) of the study. It’s a weakness of, or non-compliance with, a control process indicating a systematic quality assurance failure which, if not resolved, has the potential to cause harm to patients or data integrity and/or organisation reputation that requires the **timely notification** and further investigation by senior management and clear timelines for resolution. Major finding examples: • Where there has been failure to comply with the regulatory requirements e.g. failure to assess and report SAEs/SUSARs/SSIs accurately and to the correct bodies. • Where there has been a significant unjustified departure from GCP e.g. failure to provide participants with a copy of their consent form or Participant Information Sheet. A combination of multiple “minor” audit findings may result in a “major” systemic audit finding, even though each of the finding are not “major”.
Minor/ Other:	Any other findings, defined as those where evidence exists that a departure from applicable legislative requirements and/or established GCP guidelines and/or procedural requirement and/or good clinical practice has occurred, but it is neither Critical nor Major. Minor/Other examples: • Where no definite document management/organisation processes are in place at site.

Once the internal audit has been completed the internal auditor will complete a draft report, inclusive of non-compliances (and associated grading), and suggested recommendations for improvements.

The draft report will be reviewed by the Lead Internal Auditor and provided to the auditee within two weeks for review ('fact check') and clarification of any potential issues regarding the non-conformance classifications and recommended actions and opportunities for improvement. This will inform the CAPA plan which outlines actions, accountable persons and due dates for completion of the tasks.

After consultation with the auditee, the report, inclusive of the CAPA will be finalised and submitted to the RCH Research Operations Director, and in the case of an MCRI-sponsored trial, MCRI Sponsorship Committee Chair for final sign-off.

NB: If there are any immediate critical findings which may have an impact on participant safety and data integrity of the study, it may be necessary to escalate these issues prior to completion of the audit. Refer to Section 5.8 of this document for the MCC escalation process.

5.6 Internal Audit Report Dissemination

The internal audit report with actionable items and corrective and preventive actions will be sent to the auditee for comments and acceptance.

The signed accepted report is filed in the REG Office / MCTC Office and the CAPA remains active until all actions are completed.

A copy of the final completed report is kept on file in the REG Office / MCTC Office.

Any critical or major findings from the internal audit will be reported to the Melbourne Children's Clinical Trial Governance Committee and / or the HREC, Sponsorship Committee.

5.7 Action Completion and Verification

Every internal audit will consist of a follow-up to verify responses have been applied to the internal audit findings' actionable items and/or that the formal corrective and preventive action (CAPA) plan had been implemented by the research team. The follow-up can be conducted by either:

- email correspondence
- remotely via video link
- on-site via a follow up internal audit

The follow-up process will be as follows:

- The auditee must provide documented evidence to demonstrate that actions are in progress or have been completed.
- The Line Manager may be asked to oversee the resolution of the issue and the auditee's response.

- The responses will be reviewed by the internal auditor and 'closed' when evidence is provided for the planned resolution.
- If the items are not resolved, an 'outstanding issues' reminder will be sent to the auditee and, if necessary, their Line Manager.
- The internal audit report and the auditee's responses will be filed for noting by the RCH HREC and in the case of an MCRI-sponsored trial, the report will be provided to the MCRI Sponsorship Committee for noting at the next monthly meeting.

5.8 Escalation Process and Conflict Resolution

The internal auditor may find items that could have a potentially significant negative impact on the:

- integrity of the results
- risks to the research subjects
- ethical acceptability of the study
- insurance coverage

The Lead Internal Auditor may escalate these items to the relevant committee or require a response from the auditee within a shorter time frame. If the items are not resolved, the HREC may request further steps are taken to address the issues.

It is acceptable for the auditee to propose different resolutions to those items on the internal auditor's action summary if a sufficient case can be made. Any complaints or discussions about the internal auditing process can be directed to the Director of Research Operations at RCH.

In the case of any dispute the reports and findings/grading will be reviewed by the Chair of the HREC and / or the MCRI Research Integrity and Governance Group as per the Clinical Research Governance and Support Handbook.

If any critical quality or safety issues are identified that are applicable to the clinical research workforce a formal 'Quality and Safety Notice' will be issued to advise staff of the requirement for improvement.

6. CORRECTIVE ACTIONS

Failure of Lead Internal Auditors, Internal Auditors or auditees to follow this SOP may result in non-compliance with standards and regulations designed to generate high quality data and protect the safety of study participants, thereby resulting in poor quality data and/or harm to participants.

Any deviation from this SOP that results in a potential risk to the integrity of the data or safety of participants is to be investigated as per MCTC061 SOP Continuous improvement: A corrective and preventive action (CAPA) plan.

7. GLOSSARY

Adverse Event

Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product or other intervention. It does not necessarily have a causal relationship with this treatment.

Adverse Reaction (AR)

Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Auditee

The person or organisation that is under examination by the internal audit. The auditee must allow the internal auditor access to all information and documentation requested during the process and provide reliable information.

Lead Internal Auditor

The person responsible for taking the leading position in facilitating the internal audit process from planning to reporting. Lead Auditors are empowers to select internal auditors for an organisation.

Internal Auditor

An independent person or organisation who performs a systematic and independent examination of research related activities and documents to determine whether trial related activities, documentation, and data management have been conducted according to the protocol, GCP and applicable regulatory requirements.

Case Report Form (CRF)

Data collection tool used to record all the protocol required information to be reported to the sponsor on each research/trial participant. The CRF may be paper or electronic.

Clinical Monitoring Plan (CMP)

In accordance with the Integrated Addendum to ICH E6 (R1) Guideline for Good Clinical Practice E6 (R2) Section 5.18.7 (that was formerly adopted by the TGA with annotations on 8 February 2018), the Sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. This plan must describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use.

Clinical Research Development Office (CRDO)

CRDO provides education and training to facilitate and increase capacity for clinical and public health research across the Melbourne Children's campus. This includes the development and implementation of Standard Operating Procedures and templates to enable researchers to conduct high quality research.

Clinical Trial

The World Health Organization (WHO) definition for 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 Trial Notification (CTN)

One of two schemes used by the Therapeutic Goods Administration (TGA) to authorise the supply of unapproved therapeutic goods, including medicines, medical devices, and biologicals, to participants participating in clinical trials in Australia.

The CTN scheme is appropriate for trials where the reviewing ethics committee has enough scientific and technical expertise to review the proposed use of the unapproved therapeutic good(s). Most investigator-initiated trials would be in this category.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor and monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory requirements. Filing essential documents at the Sponsor site and participating trial sites also assists with the successful management of the trial.

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.

Human Research Ethics Committee (HREC)

A body which reviews research proposals involving human participants to ensure that they are ethically acceptable and in accordance with relevant standards and guidelines. The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

International Conference on Harmonisation (ICH)

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

Inclusion and Exclusion criteria

- Inclusion criteria - A list of conditions, that individuals must meet, in order to be eligible to participate in the study.
- Exclusion criteria - A list of conditions, any of which will exclude the person from participating in the study.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. There are four types of Investigator roles used to describe Investigators with different levels of responsibility for the conduct of clinical trials. These are described below.

Associate Investigator

Any individual member of the clinical trial team designated and supervised by the Principal investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). May also be referred to as sub-investigator.

Coordinating Principal Investigator (CPI)

If a study is conducted at more than one study site, the Principal Investigator taking the additional responsibility for coordination of the study across all sites in a region is known as the Coordinating Principal Investigator (CPI). This role applies to externally sponsored studies where the Sponsor may be a collaborative research group, commercial Sponsor or an institution. The Principal Investigator at each site will retain responsibility for the conduct of the study at their site.

Principal Investigator

The PI is the person responsible, individually or as a leader of the clinical trial team at a site, for the conduct of a clinical trial at that site. As such, the PI supports a culture of responsible clinical trial conduct in their health service organisation in their field of practice and, is responsible for adequately supervising his or her clinical trial team.

The PI must conduct the clinical trial in accordance with the approved clinical trial protocol and ensure adequate clinical cover is provided for the trial and ensure compliance with the trial protocol.

Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a participant. The term does not include any person other than an individual (eg, it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Investigator-Initiated Trials (IITs)

A clinical trial which is initiated and organised by an Investigator i.e. an individual rather than a collaborative group, company, or organisation. In these cases, the Investigator will take on the role of the trial sponsor and will then be responsible for the extensive GCP and regulatory requirements associated with both the management and conduct of the trial.

Investigational Medicinal Product (IMP)

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigational Medical Device (IMD)

A device that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.

Low / Negligible Risk (LNR)

Negligible Risk:

Research in which there is no foreseeable risk of harm or discomfort, and any foreseeable risk is of inconvenience only.

Low Risk:

Research in which the only foreseeable risk is one of discomfort

Melbourne Children's Campus (MCC)

The campus encompassing all staff from The Royal Children's Hospital, Murdoch Children's Research Institute and Department of Paediatrics University of Melbourne who initiate or carry out research under one or more of these institutional affiliations.

Melbourne Children's Trials Centre (MCTC)

Melbourne Children's Trials Centre (MCTC) is a collaboration between the Royal Children's Hospital, The Murdoch Children's Research Institute, The Royal Children's Hospital Foundation and The University of Melbourne. This Centre brings together expertise in research, clinical practice, and education and incorporates anyone who initiates or carries out research under one or more of these institutional affiliations.

Monitor

A person appointed by the Sponsor to undertake the role of monitoring for the trial. Monitors should be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately.

Murdoch Children's Research Institute (MCRI)

An Australian paediatric medical research institute located in Melbourne, Victoria, affiliated with the Royal Children's Hospital and the University of Melbourne. The institute has six research

themes: cellular biology, clinical sciences, genetics, infection and immunity, population health, and data science.

National Health and Medical Research Council: (NHMRC)

An independent statutory body within the portfolio of the Australian Minister for Health and Ageing responsible for allocating funding for, and directing, health and medical research, ethics and advice.

Non-Compliance Report Form

Used by sites participating in MCRI-sponsored IITs to report non-compliance with protocol or GCP to the Sponsor-Investigator/CPI when their assessment suggests a serious breach has occurred.

Non-Compliance Review Form

Used by Sponsor-Investigator/CPI to review non-compliance report Forms submitted by participating sites. This form documents the review and assessment of whether the Sponsor-Investigator/CPI determines the non-compliance to meet the definition of a serious breach.

Participant

A participant is a person that is the subject of the research.

Participant Information and Consent Form (PICF)

The PICF provides information about research and its requirements so that the prospective participant can decide if they wish to take part in the research. In general, this includes the purpose, methods, demands, risks, and benefits of the research. It must provide information to participants in a concise format that they are likely to understand. It must be participant centred.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial.

Protocol Deviation

A protocol deviation is any breach, divergence or departure from the requirements of GCP or the clinical trial protocol.

Research Ethics and Governance Office (REG)

REG supports the HREC and institutional research governance processes at MCRI.

Royal Children's Hospital (RCH)

The Royal Children's Hospital is major specialist paediatric hospital in Victoria, the Royal Children's Hospital provides a full range of clinical services, tertiary care, as well as health promotion and prevention programs for children and young people. Its campus partners are the

Murdoch Children's Research Institute and The University of Melbourne Department of Paediatrics, which are based on site at the hospital.

Serious Breach

A breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree: a) The safety or rights of a trial participant, or b) The reliability and robustness of the data generated in the clinical trial. Note: this guidance's definition of serious breach differs from the definition in the Australian Code for the Responsible Conduct of Research and is about deviations from the requirements of Good Clinical Practice or the clinical trials protocol.

Significant Safety Issue (SSI)

A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability of the trial.

Sponsor

An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. For investigator-initiated trials, MCRI or RCH will act as the Sponsor but delegate many sponsor responsibilities to the Coordinating Principal Investigator. In this case the CPI has the role of both Sponsor and Investigator and hence the MCTC has adopted the term **Sponsor-Investigator** to reflect the dual role of the CPI in investigator-initiated trials.

Standard Operating Procedure (SOP)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Study Team

Refers to the extended group of people involved in a research study. This includes the investigator team and any additional members of staff who are involved in the set-up or conduct of the study e.g. research nurse, research assistants.

Suspected Breach

A report that is judged by the reporter as a possible serious breach but has yet to be formally confirmed as a serious breach by the Sponsor.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

This is a serious adverse event:

- Where there is at least a reasonable possibility of a causal relationship between an intervention and an adverse event (in other words the relationship of the SAE to the trial drug/device/other intervention cannot be ruled out)

and

- That is unexpected, meaning that the nature or severity of the reaction is not consistent with the known scientific information (e.g. Investigator's Brochure for an unapproved

investigational product or product information document or similar for an approved, marketed product)

Unexpected Adverse Reaction (UAR)

An adverse reaction, the nature or severity of which is not consistent with the Reference Safety Information (RSI).

Urgent Safety Measure (USM)

A measure required to be taken to eliminate an immediate hazard to a participant's health or safety.

Quality Assurance (QA)

Covers all policies and systematic activities implemented within a quality system. QA ensures that data are recorded, analysed, and recoded in accordance with the protocol and GCP. The use of GCP guidelines ensures ethical and scientific quality standards for the design, conduct, recording, and reporting of HREC approved clinical trials that involve research participants.

8. REFERENCES

ICH GCP E6 R2

NHMRC National Statement on Ethical Conduct in Human Research (2023)

NHMRC Australian Code for the Responsible Conduct of research (2018)

MCC Clinical Research Governance & Support Handbook

Research Policy - Responsible Conduct of Research at Melbourne Children's

9. COLLABORATORS

- RCH Research Governance Office (REG)
- RCH Research Operations
- MCRI Clinical Research Development Office (CRDO)

10. RELATED DOCUMENTS

MCC Internal Audit Schedule

MCC Internal Audit Report Template

MCC Internal Audit Checklist Template

MCC Correspondence to Auditees Template

DOCUMENT END