National Mutual Acceptance
Single Ethical Review of Multi-centre Human Research Projects

MONITORING AND REPORTING FRAMEWORK

Australian Capital Territory
New South Wales
Queensland
South Australia
Victoria
Western Australia

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Contents

Section 1: Preamble

1.1 Background

National Mutual Acceptance (NMA) commenced in 2013 as a national system for mutual acceptance of ethical and scientific review for multi-centre clinical trials conducted in public health organisations. Australian Capital Territory, New South Wales, Queensland, South Australia, Victoria and Western Australia currently participate in NMA; other jurisdictions may join the system in the future.

In December 2015, the scope of NMA expanded to include all multi-centre human research projects conducted in publicly funded health services in the participating jurisdictions.

Mutual acceptance is where a proposal for a multi-centre human research project is ethically and scientifically reviewed once only by a Public Health Organisation Human Research Ethics Committee (HREC) that has been certified by the NHMRC. The exception is for those projects that require specialist review.

Under NMA, a researcher can make an application for ethical and scientific review of a human research project using the Human Research Ethics Application (HREA) through the existing application processes in the jurisdiction in which the application will be reviewed. Application for site authorisation will be through the existing research governance systems in each jurisdiction.

1.2 Introduction

This framework is intended as a guide for HRECs, organisations, researchers and other parties participating in NMA.

Additional references that relate to monitoring and reporting on human research conduct are the *National Statement on Ethical Conduct in Human Research* (National Statement) (NHMRC,2007), the *Australian Code for the Responsible Conduct of Research* (The Code) (NHMRC, 2007) and *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods* (NHMRC, 2016).

Other relevant references include:

- The *Note for Guidance on Good Clinical Practice* (CPMP/ICH/135/95) annotated with TGA comments, especially section 5.18 (TGA Note).
- *Access to unapproved therapeutic drugs – clinical trials in Australia*.
- *Human Research Ethics Committees and the therapeutic goods legislation*, 2001 extract that notes an HREC and institution may adopt appropriate monitoring mechanisms.

Separation of ethics review from research governance is relatively recent and The Code and the National Statement were not specifically designed to account for separation of these processes. For example, wording of the National Statement refers to the institution within the context of ethics review and research occurring at the same site. However, multi-centre research undergoing single ethical review in a streamlined system involves one HREC approval for research conducted at all institutions whether they are at the same or an external site.

Streamlined single ethical review of multi-centre research requires shared responsibility where:
• the HREC has responsibility for ***ethical conduct*** of research at all the sites (institutions); and
• institutions have responsibility for research governance and the ***conduct of research***.

This framework is designed to assist understanding of monitoring and reporting processes involved in ethical review and research governance of human research. It provides an overview of monitoring and reporting for human research projects and sets out the responsibilities of researchers, sponsors, Human Research Ethics Committees (HRECs) and institutions in the operation of mutual acceptance.

Section 2: Monitoring

The Code provides a guide to institutions and investigators regarding responsible research practices. The Code describes the principles and practices for responsible conduct of research and guidance for resolving allegations of research misconduct and breach of The Code, but does not provide practical advice to achieve this end.

The Code outlines how the conduct of research should be managed to ensure:
- quality, including retention of materials and research data;
- safety at the institution's site(s);
- privacy;
- risk management;
- financial management;
- compliance with laws, regulations, guidelines and codes of practice;
- contractual arrangements both internal and external;
- guidance and training for investigators;
- intellectual property;
- authorship and publication practices;
- well-defined processes for dealing with allegations of research misconduct; and
- regular monitoring of the institution's performance against The Code.

The National Statement describes monitoring as the process of 'verifying that the conduct of the research conforms with the approved proposal' and describes the mechanisms for monitoring to include:
- 'reports from researchers;
- reports from independent agencies (such as data and safety monitoring board);
- review of adverse event reports;
- random inspections of research sites, data, or consent documentation; and
- interviews with research participants or other forms of feedback from them'.

The obligations regarding monitoring for researchers and institutions can be found in Chapter 5.5 and Chapter 3.3 section 3.3.19-3.3.22.

Monitoring on matters relating to the safety and welfare of participants is set out in *Human Research Ethics Committees and the Therapeutic Goods Legislation (June 2001)* published by the Therapeutic Goods Administration (TGA). The TGA recommends that HRECs have defined mechanisms that require researchers to advise them of:
- any serious unexpected adverse events, including those that occur at other sites involved in the project;
- any new information that may have an impact on the ethical acceptability of the project or indicates the need for an amendment to the protocol;
- deviations from, or changes to, the protocol that eliminate immediate hazards to participants, affect the conduct of the project or increase risks to the participants.

The *TGA Note on good clinical practice* (section 5.18) sets out the monitoring responsibilities of sponsors to ensure projects are adequately monitored, including on-site visits.

Access to unapproved therapeutic drugs – clinical trials in Australia outlines that the HREC has an ongoing monitoring role once it approves a clinical trial protocol.

Human research ethics committees and the Therapeutic Goods Legislation, 2001 extract notes an HREC and institution may adopt appropriate monitoring mechanisms.

2.1 Investigator responsibilities for monitoring

Investigators are in the best position to monitor research first hand. As a result of monitoring, investigators must report matters relating to the ethical conduct of research to the reviewing HREC or report other matters to the institution.

Researchers should always provide comment on the implications that any new information may have on the project.

If investigators identify concerns related more broadly to the *conduct of research* (e.g. authorship, publications, etc.) the institution's research governance framework should have defined processes for addressing the issues.

Any monitoring documents that are forwarded to the HREC are often required by the Research Governance Officer for consideration from a governance perspective (e.g. there may be resourcing issues if an amendment is required). If site specific assessment requires amendment then the Research Governance Officer would administer this process.

2.2 Clinical trial sponsor responsibilities for monitoring

Clinical trial monitors, appointed by the sponsor, must ensure that trials are adequately monitored and act as the main link between the sponsor and the Coordinating Principal Investigator. Responsibilities include verifying, ensuring, informing, and communicating about the multiple and complex elements of a clinical trial. Provision of monitoring reports to the sponsor is an important component of informing the sponsor about the clinical trial.

In the case of a Contract Research Organisation (CRO) acting as the 'local' sponsor, the actions of the monitor have a vital role in informing the pharmaceutical company sponsoring the trial.

Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (NHMRC, 2016) describes the sponsor's responsibilities regarding safety.

2.3 Institutional responsibilities for monitoring

The tool for institutions to manage the monitoring of research is a **research governance framework**. Institutional research governance includes all aspects of research activity. Research ethics and site specific assessment are components of research governance.

The Research Governance Officer will administer the institutional responsibility of ensuring that research is reliably monitored. This may involve:

- mechanisms such as site auditing for research governance; and
- review of reports the HREC has received to determine whether any changes should be made regarding the site specific assessment for a project.

The New South Wales Health Research Governance Framework summarises the principles, standards and requirements for the responsible conduct of quality research. It also clarifies the responsibilities and accountabilities of key parties involved in research taking place in NSW Public Health Organisations. It is available at: http://www1.health.nsw.gov.au/PDS/pages/doc.aspx?dn=GL2011_001.

SA Health's *Research Governance Policy Directive* provides the overarching policy framework for the responsible conduct of research across SA Health. Further information on research ethics and governance is available at: www.sahealth.sa.gov.au/researchethics.

WA Health's Research Policy Framework specifies the mandatory research governance policy and standard operating procedures that must be complied with in order to ensure effective and consistent research activity across the WA health system. It is available at: https://rgs.health.wa.gov.au/Pages/Research-Governance-Framework.aspx

2.4 HREC responsibilities for monitoring

The National Statement Chapter 5.5 addresses monitoring of approved research and the responsibilities of the institution. Some monitoring is delegated to the HREC and includes responsibility for:

- ethical conduct of approved research; and
- safety and welfare of the participants.

Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (NHMRC, 2016) notes that 'The sponsor, through their independent safety monitoring arrangements, has the primary responsibility for monitoring the ongoing safety of the investigational medicinal product. The HREC should be satisfied that the sponsor's arrangements are sufficiently independent and commensurate with the risk, size and complexity of the trial'.

The HREC should:

- assess the safety of the trial and ensure that the sponsor has adequately addressed identified risk
- ensure that the sponsor's ongoing safety monitoring arrangements are adequate
- review the informed consent taking into account new information about risks and benefits
- assess whether risk/benefit complies with continued ethical approval (sponsor being responsible for proactive monitoring of the risk-benefit ratio)
- advise the TGA, investigators and relevant institutions of withdrawal of approval

The HREC has reporting mechanisms aligned with monitoring; these are described in Section 3. Reporting mechanisms regarding conduct of research, apart from research ethics, should be a matter of following the institution's research governance framework.

Section 3: Reporting

Reporting is the mechanism by which the outcome of monitoring the research is conveyed to an HREC and institution.

Reporting arises as a requirement of the National Statement, legislative and therapeutic products regulation. Reporting refers to the communication of information to a HREC and institution about the progress, safety and modification to the approved research that may arise from time to time.

A clarification of responsibilities for monitoring and reporting of safety for clinical trials is published in *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods* (NHMRC, 2016). It describes responsibilities of those involved in reporting on clinical trials of therapeutic products.

Reporting requirements regarding the progress of research will be determined by the reviewing HREC and is usually on an annual basis (or more frequently, depending on the risk) to inform the HREC and institution that conduct of the research is on track. Reporting may also arise from monitoring of research by the investigator(s) and this may result in an adverse event/serious adverse event report and consequent amendment to the research. Amendments arise for a variety of reasons and are frequent throughout the life of a research project.

The TGA Note refers to reporting in relation to a clinical trial. In this document, 4.11 Safety Reporting, there is an emphasis on the responsibility of researchers reporting to the sponsor and regulatory authorities.
NHMRC-registered HRECs require reports regarding research that has been approved by the HREC, whether the research is being conducted at the HREC's institution or another institution.

3.1 Types of reports

Safety reports
Interventions and therapies such as clinical trials, non-clinical trials and innovations require monitoring to be commensurate with risk, size and complexity of the project and the reporting to the HREC should be appropriate and in accordance with the risk.

There are a number of safety reporting mechanisms including adverse events, serious adverse events, Serious Unexpected Suspected Adverse Reactions, and data safety monitoring board reports. Details of safety event types are in *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods* (NHMRC, 2016).

Amendments
As a result of reporting of adverse events, safety reports or other activities an HREC may decide that an amendment of the approved research is required. Amendments may occur as a consequence of the reporting process or other circumstances.

In the case of multi-centre projects the Coordinating Principal Investigator (or Lead Investigator) will be the contact for amendments that may be initiated by an Investigator or a sponsor.

Protocol deviation or violation, or serious breach

Monitoring research may result in submission of a protocol deviation or violation, or serious breach report and require HREC consideration. This should be reported if there is a breach of the protocol or Good Clinical Practice (GCP) that is likely to affect to a significant degree either the safety or rights of a participant; or the reliability and robustness of the data generated in the project. The outcome of such a report may result in action by the HREC or by the institution to address misconduct of the research if the breach is serious.

3.2 Investigator responsibilities for reporting

According to the National Statement the investigator is required to have processes in place for monitoring appropriate for the research and investigators should report events or outcomes to the reviewing HREC. At all sites participating in the project, Principal Investigators should report to their relevant institution and take prompt steps to deal with any unexpected risks.

Reporting requirements will be dependent on risk and the conditions of ethical approval, and apply to any institution (site) where a reviewing HREC has provided ethics approval. Information for each jurisdiction is available in the *Monitoring and Reporting Tables* which accompany this document.

Where the investigator is also fulfilling the role of project sponsor, as in the case in investigator-initiated human research projects, refer to Section 3.3 for additional responsibilities.

3.3 Sponsor responsibilities for reporting

Sponsors have a significant role in supporting Investigators to meet their obligations for safety reporting to their Institutions and HRECs. The role and responsibilities of the sponsor are outlined in *Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods* (NHMRC, 2016).

In investigator or collaborative group sponsored projects, responsibility for reporting adverse reactions to the TGA rests with the investigator or collaborative group (*Australian Requirements and Recommendations for Pharmacovigilance Responsibilities of Sponsors of Medicines*, August 2013).

3.4 Institutional responsibilities for reporting

Separation of research governance from the ethics review process requires each institution to undertake independent site specific assessment and be informed of the proposed research and to manage the risk of conducting that research at the site(s).

Reporting processes for research governance purposes will be determined by the institution where the research is to be conducted.

Institutions may also have requirements for reporting to external bodies, regulatory authorities or government as specified in Health Department and State or Territory policies.

3.5 HREC responsibilities for reporting

Under the National Statement, the review body should maintain a record that includes the 'mechanisms to be used to monitor the conduct of the research'. The HREC needs to inform the investigator of the requirements of the HREC regarding:

- progress reports (may be annual or more frequent);
- safety and/or adverse event reports;
- any serious breach;
- amendments; and
- any unexpected risks.

Any device incidents should be reported to the Therapeutic Goods Administration (TGA) by the sponsor.

An annual report from HREC to NHMRC is a requirement in fulfilment of NHMRC certification.

Section 4: Responsibilities of Researchers, HRECs and Institutions

The *Monitoring and Reporting Tables* associated with this framework provide an overview of the requirements of Australian Capital Territory, New South Wales, Queensland, South Australia, Victoria and Western Australia in relation to:

- time frame for reporting;
- format required;
- number of copies required; and
- to whom the report is submitted.

Under NMA, researchers will be required to follow the reporting requirements of the jurisdiction in which the HREC is based.

References

National Statement on Ethical Conduct in Human Research (2007), developed jointly by National Health and Medical Research Council and Australian Vice-Chancellors' Committee.
https://www.nhmrc.gov.au/guidelines-publications/e72

Australian Code for the Responsible Conduct of Research 2007, revised jointly by the National Health and Medical Research Council and Australian Vice-Chancellors' Committee.
www.nhmrc.gov.au/guidelines/publications/r39

Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), developed by the International Committee on Harmonisation and this version refined by the Therapeutics Goods Administration.
www.tga.gov.au/publication/note-guidance-good-clinical-practice

Access to unapproved drugs – Clinical trials in Australia, developed by the Therapeutics Goods Administration.
www.tga.gov.au/publication/access-unapproved-therapeutic-goods-clinical-trials-australia

Human Research Ethics Committees and the Therapeutic Goods Legislation - June 2001 published by the Therapeutic Goods Administration (TGA).
www.tga.gov.au/publication/human-research-ethics-committees-and-therapeutic-goods-legislation

*Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (*NHMRC, 2016)
www.nhmrc.gov.au/guidelines-publications/eh59

Research Governance in NSW Public Health Organisations, GL2011_001 (2011), NSW Department of Health.
http://www1.health.nsw.gov.au/PDS/pages/doc.aspx?dn=GL2011_001

Note for guidance on clinical safety data management: definitions and standards for expedited reporting (CPMP/ICH/377/95) Annotated with TGA comments.
www.tga.gov.au/publication/note-guidance-clinical-safety-data-management-definitions-and-standards-expedited-reporting

Australian Requirements and Recommendations for Pharmacovigilance Responsibilities of Sponsors of Medicines, August 2013
www.tga.gov.au/publication/australian-pharmacovigilance-requirements-and-recommendations-medicine-sponsors