



Australian Government
National Health and Medical Research Council

N|H|M|R|C



Framework for Monitoring:
Guidance for the national approach to single
ethical review of multi-centre research

January 2012

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Electronic document

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Introductory comment

BACKGROUND

In October 2006, the Australian Health Ministers' Advisory Council (AHMAC) agreed to the establishment of a nationally harmonised approach to scientific and ethical review of multi-centre health and medical research. At the request of AHMAC, the National Health and Medical Research Council (NHMRC) took on the role of facilitating a de-centralised model of in-common policies and processes to encourage single ethical review through the Harmonisation of Multi-centre Ethical Review (HoMER) initiative. A critical element of this nationally harmonised approach is the articulation, development and promulgation of a consistent approach to monitoring arrangements for multi-centre human research that has undergone a single ethical review.

Under the nationally harmonised approach, multi-centre research projects are subject to a single ethical review by a Human Research Ethics Committee (HREC) at a certified institution. If the project is approved, that ethical approval is then adopted by participating institutions.¹ A research project that has been ethically approved is also subject to site assessment by institutions wishing to participate in the research, each of which must authorise the project before it can proceed at its site/s.² Once a research project has been approved and authorised, its conduct must then be overseen by multiple parties. Thus, the establishment and application of consistent and coordinated monitoring processes are critical to ensuring the integrity of multi-centre research.

PURPOSE OF THIS DOCUMENT

The purpose of this document is to provide a framework for best practice in the monitoring of multi-centre human research that has undergone a single ethical review. Whilst its recommendations do not equate to requirements imposed on any party, it is expected that it will influence the establishment of standards that can be used for monitoring human research in Australia, whether or not that research is health or medical research and whether it takes place at multiple centres or at a single site.

This document explores conceptions of monitoring, outlines activities that require monitoring by HRECs, institutions and researchers and proposes a suggested allocation of monitoring responsibilities. Whilst many of the elements of the Framework are already in place or can be implemented immediately, further development of some mechanisms and standard tools for implementing the framework will be required.

Professional judgement is involved in the interpretation of this guidance document, as no single document adequately captures the full range of legislation, standards and guidelines that apply to monitoring human research. Good practice in monitoring research depends on those with monitoring responsibility being appropriately skilled and experienced and working in an environment that enables them to use their professional judgement effectively.

This document does not replace existing national guidance documents or override any jurisdictional administrative and/or statutory requirements. These documents are listed in [Appendices A](#) and [B](#).

1 The term institution is used broadly to mean a research institution, organisation or, in certain cases, individuals or jurisdictions (States and Territories of Australia), either in the public or private sector, under whose authority research is conducted. The role of the institution in monitoring multi-centre research and the phenomenon of monitoring multi-centre research that takes place outside of the context of traditional institutions are discussed in later sections of this document.

2 Note that, in at least one jurisdiction, formal authorisation for commencement of research rests with an individual or body outside of the institution. However, even in that circumstance, individual sites must still conduct an assessment of the project and recommend it, or not, for authorisation.

Introductory comment

The unique issues around monitoring of research relating to specific population groups, such as Aboriginal and Torres Strait Islander peoples, and research in remote communities are not discussed in this document. Thus, adherence to this Framework alone is not sufficient for research involving Aboriginal and Torres Strait Islander peoples. A separate body of work is underway as part of the HoMER initiative relating to research involving Aboriginal and Torres Strait Islander communities. The following NHMRC publications should also be referred to:

- *Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research* (NHMRC 2003)
- *Statement on Consumer and Community Participation in Health and Medical Research* (NHMRC and Consumers' Health Forum of Australia Inc, 2002)

HOW TO USE THIS DOCUMENT

This document will be of assistance to institutional managers and administrators supporting research ethics and their colleagues supporting research governance activities. It aims to provide researchers engaged in multi-centre human research with a better understanding of monitoring activities that must be addressed after research has commenced.

An institution should have specific policies and procedures in place relating to its monitoring of all research, whether multi-centre or single site. This document provides a reference against which an institution can compare its internal administrative practices, recognising that monitoring of single site research has a high degree of overlap with monitoring of multi-centre research. As indicated, this document is recommending best practice in this area and institutions are encouraged to regularly review their monitoring and research governance policies, particularly if they are interested in applying for certification under the HoMER initiative.

Resources for information about jurisdictional level research monitoring practices in public health organisations are listed in [Appendix A](#).

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1. The place of monitoring in the oversight of human research

In recent years, the imperative to properly oversee the conduct of human research in Australia has generated frameworks for governance of research at jurisdictional and institutional levels.³ These research governance frameworks generally include recognition that assurance of appropriate ethical review and monitoring of research are components of a broader responsibility for oversight of research at the institutional and/or jurisdictional level and are activities performed in order to satisfy an overarching research governance framework. It is now clearly understood that, for research that will be conducted at more than one site, both a HREC and each participating institution must assess a proposed project and, if appropriate, provide ethical approval (HREC) and project authorisation (institution). However, there is considerable ambiguity regarding which party is responsible for monitoring which component of an authorised research project. This confusion is partly the result of an attachment to models of monitoring that precede the development of a robust concept of research governance and the development of single ethical review initiatives at the state and national level.

The evolution of the concept and scope of research governance and the advent of models of single ethical review mean that some of the monitoring responsibilities that may have been previously undertaken by a HREC are now best understood as the responsibility of the institution where the research is being conducted. This approach is also consistent with the *National Statement on Ethical Conduct in Human Research (2007)*, which states, at section 5.5, that responsibility for ensuring that research is monitored lies with the institution under whose authority the research is conducted. Further, the responsibilities delineated and allocated in this Framework are described as 'monitoring responsibilities' whether or not they have traditionally been categorised as such. Whilst this approach expands the traditional definition of monitoring as found in some guidelines and regulations, it more accurately reflects the reality of monitoring the conduct of a research project where multiple parties have responsibility for the oversight of human research.

1.1 PARTIES RESPONSIBLE FOR MONITORING HUMAN RESEARCH

Parties responsible for the oversight of multi-centre human research include researchers, institutions, reviewing HRECs and sponsors of research, including any expert committees that may be established to assist any of these parties in the fulfilment of their responsibilities. For some types of complex research, regulatory agencies may also be involved in monitoring activity. The separate and overlapping responsibilities for each of the various components of monitoring will be described in later sections of this document; however, the emphasis will necessarily be placed on the reviewing HRECs and authorising institutions, whose monitoring roles and responsibilities are the least clearly distinguished and the most likely to overlap.

Delegation of monitoring responsibilities within an institution takes place within the parameters of that institution's research governance Framework and may include delegating responsibility for discrete aspects of monitoring to oversight committees, experts within the organisation or administrative staff.⁴ Delegations of this kind are necessary and should be supported. Historically,

³ The NHMRC, via its HoMER initiative, has also developed the *Research Governance Handbook: Guidance for the national approach to single ethical review* which should be read in conjunction with this document. Several Australian states and research-interested organisations have also developed guidance in research governance in the form of frameworks, toolkits or policy statements. For more information, see the resource section at the end of this document.

⁴ Reference to committees, including HRECs, should always be understood as including the committee membership, its Chair, any associated sub-committees and the committee's administrative support staff.

1. The place of monitoring in the oversight of human research

these delegations commonly included the delegation of significant monitoring responsibility to the institution's HREC, based on its knowledge of the project gained by virtue of having conducted a review of the project. Single ethical review changes this model. Under single ethical review of multi-centre research, only one HREC reviews a research project and, as a consequence, local (mostly institutionally-based) HRECs no longer have knowledge of the project, with the notable exception of the one HREC that conducted the review. Therefore, only the reviewing HREC can take on those elements of monitoring a research project that are attributable to HRECs. The outcome of this logic, which is a foundational principle of this Framework, is that HRECs that do not review a research project have no monitoring role with respect to that project and cannot accept the delegation of responsibility from an institution to perform such a role.

1.2 TIMELINE FOR MONITORING OF RESEARCH PROJECTS

Prior to authorisation of a research project, oversight includes developmental aspects of the research (including commercial aspects, when relevant), ethical and scientific review and assessment of the project by participating sites (sometimes referred to as "governance review"). As described earlier, based on site assessment and ethical approval, a project may then be authorised by either the participating institutions or a jurisdictional body such as a health district, area health service or local health network. Responsibility for monitoring a research project begins upon authorisation of the project and continues through all phases of the conduct of the research project, including the closure of the research project and, as described below, in some cases even beyond the cessation of activity related to the project *per se*.

An illustration of the timeline for monitoring research can be drawn from the various types of reports that are traditionally considered requirements associated with the conduct of a research project. These reports include: safety reports, progress reports, annual reports (a form of progress reporting) and final reports. As described below, matters such as communication of individual research results and publication of outcomes, both of which generally occur after the closure of a research project, can also be considered subject to monitoring and are included as components of monitoring in this Framework.

2. National and international guidance and regulation

The identification and allocation of monitoring responsibilities related to research conducted in Australia is derived from a set of regulatory provisions, national and international codes and guidelines promulgated by the Australian government and higher education authorities. Policies and guidelines established by Australian States and Territories are also, to differing degrees, either binding or persuasive. These authorities and authoritative documents include:

- (the) *National Statement on Ethical Conduct in Human Research*, 2007 (National Statement);
- (the) *Australian Code for the Responsible Conduct of Research*, 2007 (Code);
- *Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research*, 2003;
- *Keeping Research on Track – a Guide for Aboriginal and Torres Strait Islander Peoples about Health Research Ethics*, 2006;
- *Code of Ethical Standards for Catholic Health and Aged Care Services*, 2001;
- *NHMRC Australian Health Ethics Committee Position Statement – Monitoring and reporting safety for clinical trials involving therapeutic products*, 2009 (AHEC position statement)
- *The Australian Clinical Trials Handbook*, 2006;
- *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) – Annotated with TGA Comments*, 2000 (GCP);
- *Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) – Annotated with TGA Comments*, 2001;
- *Access to unapproved therapeutic goods – clinical trials in Australia*, 2004;
- *Therapeutic Goods Act*, 1989; and
- *Therapeutic Goods Regulations*, 1990.

Various States and Territories of Australia have developed guidelines and policies for monitoring that either replicate or expand upon the authoritative documents listed above and which are reliant upon these documents for their underlying authority, as well as reflecting existing State or Territory legislative or regulatory provisions. Individual research institutions and professional research organisations have also developed guidelines and policies that derive their authority from these documents.

The *National Statement* is directed to institutions, HRECs and researchers, whereas the Code is directed primarily to institutions and researchers and is about research governance more generally. TGA requirements are directed principally to researchers and research sponsors. Good Clinical Practice guidance (GCP)⁵ is directed toward all parties, as is the AHEC Position Statement.

Although these documents differ somewhat in emphasis and specifics between themselves and other authoritative sources, all of the authoritative sources attribute the broad responsibility for monitoring research to the institution in which the research is conducted, with the added (complementary and primary) responsibility for unapproved therapeutic goods assigned to sponsors of clinical trials involving those substances. Oversight of conformance to a research protocol is designated as a primarily HREC responsibility.

Whilst this document does not include excerpts from or direct citation to these guidelines and regulations, links to the major sources of authority are provided at the end of the document.

⁵ GCP was originally developed to apply to commercially-sponsored international drug trials. Its application has gradually been extended to cover all drug trials and, by some people's reckoning, to all clinical research.

3. Monitoring role of the reviewing HREC

Traditionally, most research monitoring activity at the site level was either understood explicitly as the responsibility of the local HREC or implicitly as an institutional responsibility delegated to its HREC. This paradigm is not consistent with the structure of single ethical review of multi-centre research and compromises the integrity of that model. As previously explained, under single ethical review of multi-centre research, HRECs that are not involved in the review and approval of a research project can have no monitoring role with respect to that project. Thus, all references to the monitoring role and responsibilities of a HREC are, by definition, referring to the role and responsibilities of the reviewing HREC.

Reviewing HRECs have a clearly defined responsibility for monitoring the conduct of a research project in accordance with an approved protocol.⁶ In order to ensure that projects that they approve are conducted ethically, the HREC must:

- ensure that it is notified of any changes to the protocol and that it has an opportunity to consider any substantive changes to the protocol that would implicate the continued ethical conduct of the project;
- have some role in protecting the safety and welfare of participants in the research via notification or review of relevant information from appropriate parties in keeping with national and local regulations, guidance and policies related to safety reporting;
- ensure that it is notified of and, where appropriate, has an opportunity to retrospectively consider protocol violations⁷ or prospectively approve requests for the waiver of a protocol requirement;
- oversee the conduct of the project via receipt of progress reports on at least an annual basis during (at a minimum) the active phases of the research project
- ensure that any agreements by researchers to communicate individual research results are honoured; and
- ensure that any special conditions that it has imposed at the time of project approval are met.

As will be explored more fully in Sections 4 and 9, other activity previously defined as ‘HREC monitoring’ (or not recognised explicitly as necessary monitoring activity) is more appropriately handled, at least initially, by institutions under a single ethical review model. The implications of this are discussed below.

The primary modes of oversight that HRECs use to monitor approved research are amendments and reports from researchers – or reports from sponsors submitted via researchers. It is noted that amendments are not a monitoring activity *per se*, but are a means of addressing and presenting proposed or necessary changes to a project. Traditionally, researchers and sponsors submit amendments and HRECs review them. As will be discussed, the single ethical review

⁶ Or, in some cases, a less formalised document commonly referred to as a ‘project description.’ The development of a ‘protocol’ to describe and govern a research project is universally required in the context of clinical trials of medical interventions and has become increasingly used in the context of other types of clinical research, basic science research and other complex human research.

⁷ The distinction between protocol violations and protocol deviations is neither clearly understood nor consistently applied amongst Australian HRECs, but, for the purposes of this document, protocol violations are those variations to a protocol that implicate participant consent, participant safety or data integrity that compromises the ethical acceptability of the project, and, thus, require retrospective notification to or review by a HREC, whereas protocol deviations relate to other matters and do not require notification to or review by a HREC. This definition is consistent with ICH/GCP taxonomy.

3. Monitoring role of the reviewing HREC

model precipitates a need for some degree of screening of amendments by administrative staff in order to determine:

- (a) which amendments must be reviewed by the HREC⁸
- (b) which amendments have implications (usually related to resources) for the participating institutions.

Similarly, reporting is not, in itself, a monitoring activity, but rather a mechanism for monitoring that is used by various parties to satisfy their monitoring obligations⁹. This also applies to annual reporting, as explored more fully below. Safety reporting is particularly complex and will also be addressed in detail below.

As will be described in the following sections, responsibility for all other monitoring activities lies primarily with other parties although, with respect to some of those activities, reports back to the HREC from institutions and sponsors, generally via researchers, may be appropriate.

8 The 'screening' of amendments is not particular to single ethical review. It is common practice in many HRECs to screen out 'administrative' amendments for consideration by administrators only and, in many HRECs, for even substantive amendments to be reviewed by the Chair or a subgroup of the full HREC, followed by ratification by the full committee.

9 The exception to this statement is that the activity of tracking whether a report has been received is, technically, a monitoring activity.

4. Monitoring role of the institution

Institutions have a substantial monitoring role and significant monitoring responsibilities.¹⁰ In accordance with the institution's research governance framework, institutions are obliged to ensure the integrity of their research programs and their researchers and the individual projects that those researchers conduct. In addition, institutions have a responsibility to protect the safety and welfare of participants in research conducted under their auspices, particularly, in the health context, those participants who are also being treated or cared for at those institutions.

Formally, the institution's role in oversight of research derives from a multiplicity of sources, including obligations as defined in the *National Statement*, *the Australian Code*, TGA and ICH/GCP guidance, and jurisdictional policies and research governance frameworks. On a more practical level, under a system of single ethical review the oversight and governance roles translate into specific institutional monitoring responsibilities as a function of the removal of all but one local HREC from responsibilities related to any multi-centre research project. Finally, by considering to whom responsibility for oversight activity that is classically considered 'monitoring' should be allocated, it becomes clear that institutions are best placed to take on related oversight responsibilities.

Thus, authorising institutions have a responsibility for monitoring the conduct of a research project in order to ensure that projects that they authorise are conducted with integrity and in compliance with relevant requirements. Consequently, each institution should:

- ensure that it exercises appropriate quality control over a research project such that researchers or other staff over whom it has authority conform to any contracts and agreements and comply with any relevant internal or applicable external policies;
- ensure that it has an opportunity to consider any changes to a research project that have implications for its capacity to support the conduct of the project in accordance with any ethical and administrative requirements;
- have some role in protecting the safety and welfare of participants in the research via notification of relevant information from appropriate parties;
- ensure that data collected and used are properly secured and that project records are properly kept.
- ensure that financial matters related to a research project (e.g. Budgets and grants) are being properly managed;
- oversee the conduct of the project via receipt of progress reports on at least an annual basis during (at a minimum) the active phases of the research project;
- oversee the conduct of the project via receipt of final reports on the research project.
- ensure that project closure proceeds in accordance with any contractual or internal site requirements;
- ensure that research outcomes that are published are notified to the institution;
- ensure that any complaints raised by participants in the research, allegations of research misconduct or potential post-project authorisation conflicts of interest are properly investigated and that any resulting recommendations are implemented and, if appropriate, notified to the reviewing HREC; and
- ensure that any special conditions that it has imposed at the time of project authorisation are met.

¹⁰ Note that an institution can sometimes function as the sponsor of a research project. In such circumstances, it is necessary to ensure that the institution segregates its two sets of responsibilities in order to ensure that they are all fulfilled.

4. Monitoring role of the institution

To carry out their oversight role, many Australian institutions have developed administrative units such as Offices of Research with dedicated staff employed for this purpose. Increasingly, State and Territory single ethical review programs and research governance frameworks and policies require the identification of a 'research governance officer.' The National Approach to single ethical review is also premised on the need for these staff. These offices and staff are well-placed to have operational responsibility for carrying out many of the institution's monitoring obligations. However, it is acknowledged that many Australian institutions have insufficient resources to meet all of their monitoring obligations and that securing these resources will require future advocacy and commitments by all members of the Australian research community.

Institutions may also choose to delegate selected monitoring responsibilities to internal or even external experts – scientific, legal or otherwise – in order to fulfil their obligations. Whilst this is appropriate, in principle, it must be emphasised that delegation to these experts should be as individual representatives or agents of the institution, not in their capacity as members of an institution's HREC, even if an institution's HREC is the HREC that reviewed a relevant research project.

5. Monitoring role of researchers

Researchers have a responsibility to ensure the integrity and ethical appropriateness of the individual projects that they conduct. This responsibility covers all aspects of the research project and is an ongoing responsibility, sometimes requiring monitoring activity long after a research project has formally closed.

The principal way in which researchers fulfil their monitoring responsibilities is via reporting to other parties or by forwarding on reports provided to them by sponsors of the research. As detailed below, different types of reports require differing reporting pathways; however, in most cases, it is the role of the researcher with primary responsibility for the project at his or her site, the 'principal investigator' or 'PI' in the health research context, to complete and submit the reports.

In the national approach to single ethical review, the researcher who has overall responsibility for the project across all sites, known as the 'coordinating principal investigator' or 'CPI', has responsibility for all communication with the reviewing HREC, in addition to his or her independent responsibilities as the PI at his or her site. Regarding his or her role with respect to the reviewing HREC, the CPI may serve as a conduit for reports or other information provided by one or more of the PIs at the participating sites or may consolidate multiple reports or compile a summary report for review by the HREC.

The monitoring role of the researcher is not merely reactive – submitting reports that are explicitly required by an institution or HREC in accordance with a pre-determined schedule, but proactive – informing appropriate parties of any matter related to the conduct of the research that merits notification to or review by one of the other monitoring parties.

6. Monitoring role of the research sponsor

Sponsors of research have a responsibility to ensure the integrity and ethical appropriateness of each research project that they sponsor, including protecting the safety and welfare of participants in their research. However, this role varies depending on the nature of the sponsorship and the nature of the research project. Sponsorship of a research project can indicate:

- a formal identity as the party that must comply with regulatory and administrative requirements imposed by national or international legal frameworks; and/or
- the party that is providing all or a major part of the funding or in-kind support for a research project; and/or
- the party that is coordinating the project across multiple centres where the research is being conducted.

Sponsors of research can be commercial companies, collaborative research groups, government entities or universities. In some instances, even in the context of multi-centre research, the sponsor of a research project is one of the institutions in which the research is being conducted.¹¹

Whilst the monitoring responsibilities of sponsors are relevant to this Framework for Monitoring multi-centre research, they are not subject to best practice recommendations of the NHMRC. For this reason, the monitoring responsibilities of sponsors that are delineated in this document are neither comprehensive nor fully articulated.

¹¹ In single site research that is not otherwise sponsored by an external party, the institution is the presumptive sponsor.

7. Other monitoring roles

HRECs, institutions or sponsors may use individuals or committees who are expert in a given area to advise them on matters related to monitoring. Whilst this practice is not restricted to the realm of safety monitoring, it is principally in this area that it arises.

7.1 SAFETY MONITORING

Many clinical trials are designed to include the input of expert committees known as Data and Safety Monitoring Boards (DSMB)¹² that review data to ascertain whether there is any cause for action to be taken to address safety concerns or other issues. Others that may perform similar roles include trial management committees, pharmacovigilance committees and individuals with appropriate expertise within an institution.

Whilst all human research need not be subject to complex safety monitoring arrangements, the following represents best practice in safety monitoring under the current regulatory regime, with recognition of the guidance provided by Australian authoritative documents:

- All proposed research should be given a risk profile¹³ by the HREC and the institution as part of their reviewing and site assessment activity;
- HRECs and institutions should identify high risk research and require researchers to specify how these risks will be addressed and monitored;
- DSMBs or equivalent independent or semi-independent¹⁴ committees should be formed for each high risk research project and its composition should be subject to review and approval by the reviewing HREC;
- Researchers should submit reports of relevant adverse events occurring at their site as required by regulation and an institution's clinical governance or research governance requirements ('upward reporting');
- The DSMBs or their equivalent should be charged with the assessment of the significance of any relevant adverse events or other safety-related information and should provide any necessary advice to researchers and sponsors regarding the safety profile of a drug or device or other relevant matters;
- In accordance with regulatory requirements, sponsors and regulatory agencies will be engaged in ongoing review of Suspected Unexpected Serious Adverse Reactions (SUSARs) and other Serious Adverse Events (SAEs) based on reports from researchers, DSMBs and each other and will make determinations as to whether action is recommended or required to address any safety issues, including modifications to the protocol, Investigators Brochure (IB) or Participant Information and Consent Form (PICF);

¹² These committees are known by a variety of similar names and acronyms. 'DSMB' is used here to represent all of the variations.

¹³ Per National Statement Chapters 2.1, 3.3.20 and 5.5.2, institutions are obliged to assess project risk in order to ensure that the level of monitoring planned and undertaken is commensurate with the degree of risk to participants in the research. It is appropriate for HRECs to make a similar assessment. Institutions also commonly engage in an assessment of institutional risk as part of their site assessment process.

¹⁴ Independence is gauged relative to an individual's relationship to a project sponsor, the research project and the research team. In many instances, it may not be possible or practical to require complete independence of all members of a committee charged with safety monitoring. With respect to each relevant research project, the degree of independence required should be determined by the HREC in collaboration with the researchers at the time of project review by the HREC.

7. Other monitoring roles

- Action recommended or required by DSMBs, sponsors or regulatory agencies should be notified to researchers. When these recommended or required actions have been integrated into amendments to the protocol, IB, PICF or other relevant document, these amendments should be submitted to the reviewing HREC for consideration;
- Individual safety reports or summaries compiled by research sponsors should be submitted directly to HRECs only in rare circumstances and institutional policies should be written or re-formulated to clarify appropriate processes for managing the submission of reports that do not need to be reviewed by the HREC ('downward reporting'); and
- Determinations made by a HREC upon review of any safety matters should be communicated to each participating site via the CPI and PIs, as necessary.

As a general principle, review of raw safety data and safety reports should ordinarily be undertaken by expert agencies, committees or individuals outside of the institution and the HREC and duplication of review or unnecessary submission of safety reports to the HREC should be avoided wherever possible.

8. Mechanisms for monitoring

8.1 REPORTING

Monitoring multi-centre research is primarily achieved via reporting and audit. Types of reporting include safety reports, progress reports, annual reports (a form of progress reporting) and final reports. Institutions may also require additional reports in satisfaction of their monitoring responsibilities.

Reporting regimes under single ethical review are necessarily different from traditional reporting schedules. Progress reports are submitted to the HREC by the CPI based on reports from PIs at individual sites. Annual reports, based on a newly created template containing a Part A (for institutions) and a Part B (for HRECs) are submitted to institutions by PIs and to the HREC by the CPI (based on collated Part B reports from project PIs), respectively. Final reports are submitted by PIs to their institutions and not to HRECs directly. HRECs are notified of the completion of a project once the project has been closed at all participating sites.

Safety reporting follows the AHEC Position Statement (May 2009 and any future iterations); however, as described above in Section 7.1, a greater emphasis is placed on reports from DSMBs or their equivalents to HRECs and PIs and both PIs and HRECs should receive a significantly reduced number of individual and summary reports.

Flow charts for reporting are presented on the following pages as Diagrams 1 and 2.

8.2 AUDITING

Auditing can be carried out by sponsors or regulatory agencies in the form of site visits. Equally, institutions or HRECs can develop audit programs that are tailored to specific needs and operate within the constraints of available resources. These programs can include comprehensive audit, spot audit, targeted or random audit or combinations of two or more of these. Some audit programs conducted by institutions or HRECs are tied to prior self-audit activity that is required of researchers. Whilst there are no recommendations offered regarding the form of auditing that is used, it is best practice in monitoring multi-centre research for both researchers and their institutions to engage in a realistic, well-designed and consistently implemented audit program. HREC auditing should remain discretionary.

8. Mechanisms for monitoring

Diagram 1
Safety Reports†

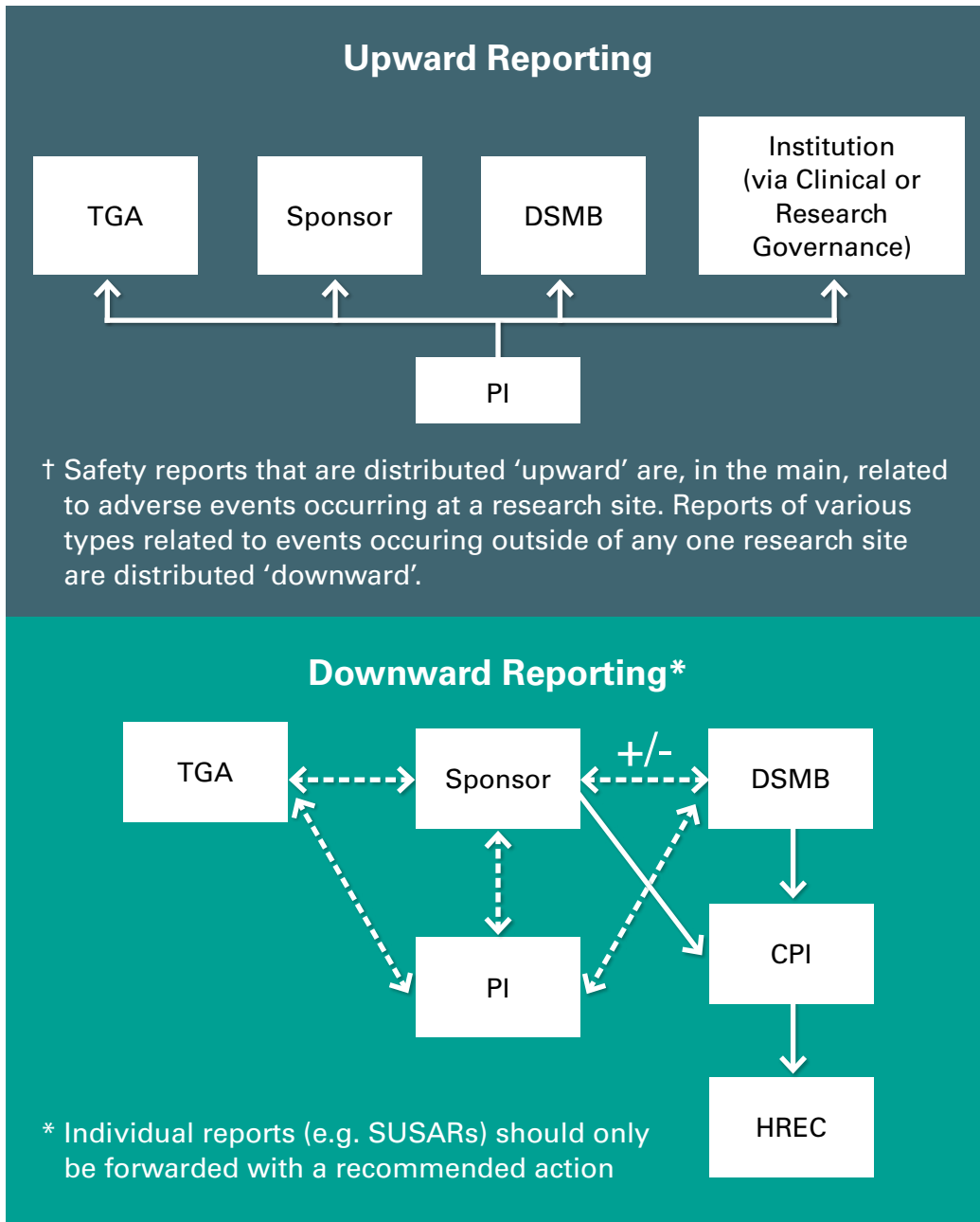


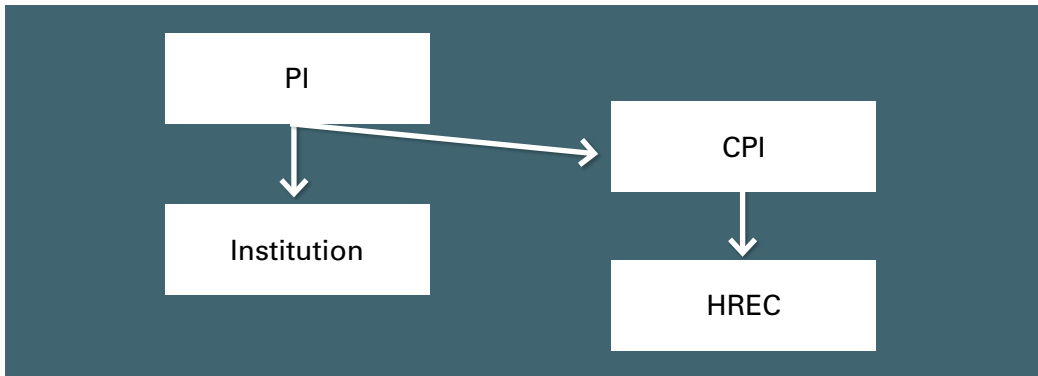
DIAGRAM KEY

- TGA Therapeutic Goods Administration
- DSMB Data and Safety Monitoring Board
- PI Principal Investigator
- CPI Co-ordinating Principal Investigator
- HREC Human Research Ethics Committee

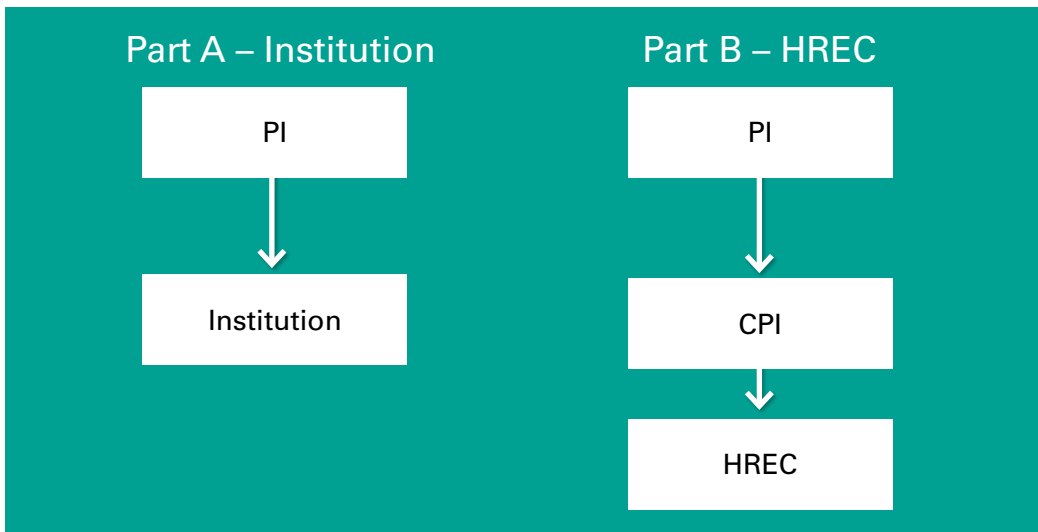


Diagram 2

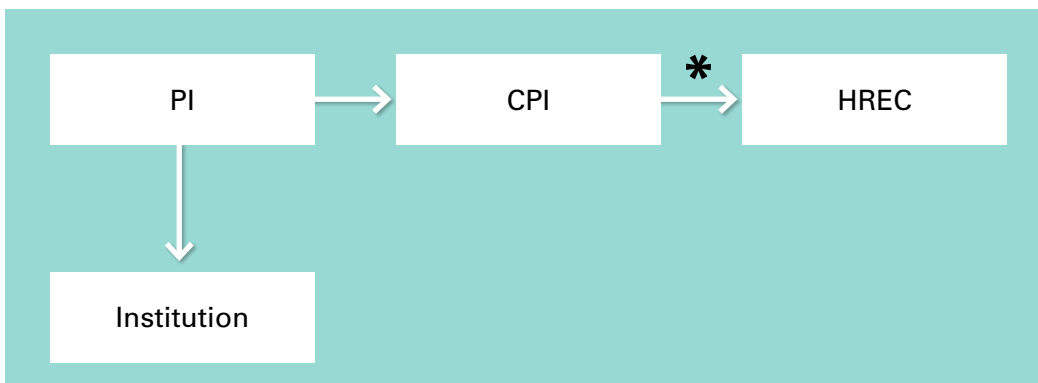
Progress Reports



Annual Reports



Final Reports



* Notification only after all sites completed

9. Allocation of monitoring responsibilities

The table below sets out the components of monitoring of multi-centre research, the parties responsible for monitoring each of these components and monitoring responsibilities of each party.

TABLE KEY

HREC = Human Research Ethics Committee (including administrative staff)

PI = Principal Investigator

CPI = Coordinating Principal Investigator

RGO = Research Governance Officer

* An institution may be an organisation or, in certain cases, an individual under whose authority research is conducted. The staff of the institution to whom monitoring responsibility is delegated is described in the institution's research governance framework.

Monitoring component/activity	Responsible parties	Monitoring responsibility	Change from status quo/per single ethical review	Comment
Conduct of project in accordance with protocol including proposed changes to protocol	CPI	<ul style="list-style-type: none"> Project coordination Submission to HREC of amendments, protocol violations, requests for waiver of protocol requirements Submission to HREC of required reports Submission to sponsor of required reports 	Introduces the role of the CPI as the party with responsibility for coordination of the project and communication with the HREC.	Whilst amendments are not technically monitoring, they are implicated in the monitoring activity of overseeing the conduct of a project to ensure that it conforms to the protocol.
	PI	<ul style="list-style-type: none"> Project management at site Communication with CPI as necessary Referral of approved amendment or other submission to institution, as appropriate 		
	HREC	<ul style="list-style-type: none"> Review of amendments and other submissions Review of required reports 		
	Sponsor	<ul style="list-style-type: none"> Review of required notifications/reports Site audit 		
	Regulatory agency	<ul style="list-style-type: none"> Review of required notifications/reports Site audit, as necessary 		

9. Allocation of monitoring responsibilities

Monitoring component/activity	Responsible parties	Monitoring responsibility	Change from status quo/per single ethical review	Comment																													
Conduct of project in accordance with institutional requirements including: <ul style="list-style-type: none"> management of resources management of finances conformance to contracts and agreements compliance with policies data security record keeping 	Institution	<ul style="list-style-type: none"> Review of amendments, as necessary Review of required reports Audit as necessary 	Monitoring by the institution becomes a more explicit and robust sphere of activity that arises out of the relationship between the PI and the institution. RGOs and Offices of Research play a critical role in this relationship.	This component includes a range of activity which has always been part of necessary oversight of research. Only institutions are positioned to monitor these activities. Pursuant to their responsibility to monitor the management of their resources, institutions may choose to assess protocol amendments that have been approved by the HREC.																													
	PI	<ul style="list-style-type: none"> Project management at site Submission to institution of required reports 			Special conditions of approval or authorisation	HREC	<ul style="list-style-type: none"> Per condition imposed 	No change	HRECs or institutions may impose special conditions of project approval or authorisation and, when imposing any condition, should also indicate how compliance is to be achieved.	CPI	<ul style="list-style-type: none"> Per condition imposed 	Institution	<ul style="list-style-type: none"> Per condition imposed 	PI	<ul style="list-style-type: none"> Per condition imposed 	Management of complaints	Institution	<ul style="list-style-type: none"> Receipt and investigation of complaints 	The institution takes on the primary role in managing complaints previously handled by either HRECs or institutions.	Complaints arise principally from those with a relationship to the institution rather than the HREC and investigation of any complaints under single ethical review is better handled by institutions, with recommendations passed on to HRECs if related to the conduct of the research project.	PI/CPI	<ul style="list-style-type: none"> Reporting to HREC based on institutional recommendations 	Management of allegations of research misconduct	Institution	<ul style="list-style-type: none"> Receipt and investigation of allegations 	The institution takes on the primary role in managing allegations previously handled by either HRECs or institutions.	Allegations of research misconduct arise with reference to employees of or individuals affiliated with an institution and investigation of allegations is best handled by institutions, with recommendations passed on to HRECs as necessary.	PI/CPI	<ul style="list-style-type: none"> Reporting to HREC based on institutional recommendations, when appropriate 	Management of conflicts of interest arising during conduct of project	Institution	<ul style="list-style-type: none"> Review of required reports Receipt and investigation of potential conflicts of interest 	The institution takes on the primary role in managing potential conflicts of interest previously handled by either HRECs or institutions.
Special conditions of approval or authorisation	HREC	<ul style="list-style-type: none"> Per condition imposed 	No change	HRECs or institutions may impose special conditions of project approval or authorisation and, when imposing any condition, should also indicate how compliance is to be achieved.																													
	CPI	<ul style="list-style-type: none"> Per condition imposed 																															
	Institution	<ul style="list-style-type: none"> Per condition imposed 																															
	PI	<ul style="list-style-type: none"> Per condition imposed 																															
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	PI/CPI	<ul style="list-style-type: none"> Reporting to HREC based on institutional recommendations 			Management of allegations of research misconduct	Institution	<ul style="list-style-type: none"> Receipt and investigation of allegations 	The institution takes on the primary role in managing allegations previously handled by either HRECs or institutions.	Allegations of research misconduct arise with reference to employees of or individuals affiliated with an institution and investigation of allegations is best handled by institutions, with recommendations passed on to HRECs as necessary.	PI/CPI	<ul style="list-style-type: none"> Reporting to HREC based on institutional recommendations, when appropriate 	Management of conflicts of interest arising during conduct of project	Institution	<ul style="list-style-type: none"> Review of required reports Receipt and investigation of potential conflicts of interest 	The institution takes on the primary role in managing potential conflicts of interest previously handled by either HRECs or institutions.	Declarations or allegations of conflict of interest arise with reference to employees of or individuals affiliated with an institution and investigation and management of any potential conflicts of interest are best handled by institutions, with recommendations passed on to HRECs as necessary.	PI/CPI	<ul style="list-style-type: none"> Reporting to HREC based on institutional recommendations, when appropriate 															
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	PI/CPI	<ul style="list-style-type: none"> Reporting to HREC based on institutional recommendations, when appropriate 																															

9. Allocation of monitoring responsibilities

Monitoring component/activity	Responsible parties	Monitoring responsibility	Change from status quo/ per single ethical review	Comment
Closure of project	CPI	<ul style="list-style-type: none"> • Submission of final notification to HREC 	The institution is responsible for project closure at its site with CPI notification to the HREC when all sites are closed.	Closure of a research project is an administrative process sometimes lasting years. HRECs have no role in this process other than receiving final notification.
	PI	<ul style="list-style-type: none"> • Completion of requirements • Notification of completion to CPI 		
	Institution	<ul style="list-style-type: none"> • Completion of requirements 		
	Sponsor	<ul style="list-style-type: none"> • Oversight of site processes per standard procedures 		
Communication of results to research participants	CPI	<ul style="list-style-type: none"> • Submission of annual report to HREC 	Introduction of coordinated monitoring by HRECs of this aspect of conduct of research.	Communication of research results to individual participants, often in the context of genetic research, is a component of conformance to a protocol and within the monitoring remit of HRECs.
	PI	<ul style="list-style-type: none"> • Project management at site • Submission of annual report (Part B) to CPI 		
	HREC	<ul style="list-style-type: none"> • Review of annual report 		
Publication of outcomes	PI	<ul style="list-style-type: none"> • Reporting to institution via annual and final reports 	Introduction of coordinated monitoring by institutions of this aspect of conduct of research.	Publication of outcomes is an event that often occurs well after project closure, is linked to final reporting and to employment issues and is thus best handled by institutions.
	Institution	<ul style="list-style-type: none"> • Review of annual and final reports 		

10. Application of the framework

10.1 PUBLIC SECTOR HEALTH RESEARCH

This Framework is most easily adapted to multi-centre health research conducted in the public sector; specifically, clinical trials conducted in that environment. However, the guidance is not applicable exclusively to that one type of research. Indeed, clinical trials are themselves a heterogeneous category of clinical research and small, multi-centre ‘investigator-initiated’ clinical trials bear little relationship to international, Phase III clinical trials sponsored by pharmaceutical companies in dozens of countries. To the extent that a health research project conducted in the public sector is characterised by the involvement of discrete institutions and has an identified CPI, this Framework can be followed. Where those characteristics are not present, it is incumbent upon researchers, the sponsor, if any, institutions and the HREC to negotiate reasonable arrangements in order to ensure appropriate and robust monitoring of the proposed research project.

10.2 PRIVATE SECTOR HEALTH RESEARCH

Application of the Framework to health research in the private sector is a challenge. To the extent that a health research project conducted in the private sector is characterised by the involvement of discrete institutions and has an identified CPI, this Framework can be followed. Where those characteristics are not present, it is incumbent upon researchers, the sponsor, if any, institutions, if any, and the HREC to negotiate reasonable arrangements in order to ensure appropriate and robust monitoring of the proposed research project. In particular, the practice of identifying a ‘de facto’ lead investigator in private sector health research may need to become more formalised, with that person taking on the responsibilities of the CPI. Further, whilst the relationship between researchers and private institutions is meaningfully different than that between researchers and institutions in the public sector, researchers are nonetheless often strongly affiliated with one or more private institutions, permitting the application of an approach to monitoring responsibility analogous to that recommended for the public sector.

Nevertheless, in private sector research, the reviewing HREC may need to take on a larger monitoring responsibility to replace absent structures or limited resources at the institutional level.

10.3 NON-HEALTH RESEARCH AND UNIVERSITY-BASED OR COMMUNITY-BASED HEALTH RESEARCH

This Framework is oriented toward moderate to high risk health research; however, the principles and general allocation of responsibility described can be applied to multi-centre non-health research. It can also be applied to multi-centre university-based health research, given the role of the university as an institution capable of performing the same monitoring functions as a public health organisation. Community-based research taking place at multiple sites or, even more diffusely, in the community at-large may be conducted under the auspices of an institution, such as a university; however, where these characteristics are not present, it is incumbent upon researchers and the HREC to negotiate reasonable arrangements in order to ensure appropriate and robust monitoring of the proposed research project.

10.4 SINGLE SITE RESEARCH

As this is a Framework for monitoring of multi-centre research, use of the Framework as a model for monitoring of single site research is discretionary. Nevertheless, there is no reason why the overall approach and the specific allocation of responsibility between HREC and institution as described in this document cannot be adopted by or adapted to research conducted at a single site.

Appendix A

MONITORING PRACTICES FOR PUBLIC HEALTH ORGANISATIONS

Australian States and Jurisdictions

NEW SOUTH WALES

NSW Health Guideline: Operations Manual: Human Research Ethics Committee Executive Officers Document Number GL2010_014 http://www.health.nsw.gov.au/policies/gl/2010/GL2010_014.html

In particular,

- Page 19 EO 009: Amendments to approved research projects
- Page 22 EO 010: Urgent safety-related measures
- Page 23 EO 011: Adverse event reporting
- Page 26 EO 012: Monitoring approved research projects
- Page 31 EO 014: Complaints about the conduct of an approved research project

NSW Health Guideline: Operations Manual: Research Governance Officers Document Number GL2010_015 http://www.health.nsw.gov.au/policies/gl/2010/GL2010_015.html. In particular,

- Page 17 RGO 008: Amendments to authorised research projects
- Page 19 RGO 009: Urgent safety-related measures
- Page 21 RGO 010: Adverse event reporting
- Page 23 RGO 011: Monitoring and oversight of authorised research projects
- Page 25 RGO 013: Complaints about the conduct of an authorised research project

QUEENSLAND

Queensland Health Standard Operating Procedures for Human Research Ethics Committees http://www.health.qld.gov.au/ohmr/documents/QH_hrec_sops.pdf. In particular,

- Page 18: Multi-centre Research
- Pages 55–61: (Section 7), HREC Monitoring of Research given Institutional Authorisation
- Page 67: (Section 10), Handling Complaints
- SF 26, 27, and 28 on pages 150–154

VICTORIA

Research governance toolkit, 2010 produced by the Victorian Managed Insurance Authority <http://www.vmia.vic.gov.au/display.asp?entityid=3023>

Appendix B

NATIONAL GUIDANCE DOCUMENTS

NHMRC

- *National Statement on Ethical Conduct in Human Research, 2007*
<http://www.nhmrc.gov.au/publications/synopses/e72syn.htm>
- *Australian Code for the Responsible Conduct of Research, 2007*
<http://www.nhmrc.gov.au/publications/synopses/r39syn.htm>
- Australian Health Ethics Committee Position Statement: Monitoring and Reporting of Safety for Clinical Trials Involving Therapeutic Products, May 2009
http://www.nhmrc.gov.au/health_ethics/hrecs/hrecalerts.htm
- *Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research, 2003* <http://www.nhmrc.gov.au/publications/synopses/e52syn.htm>
- *Keeping Research on Track – a Guide for Aboriginal and Torres Strait Islander Peoples about Health Research Ethics, 2006* <http://www.nhmrc.gov.au/publications/synopses/e65syn.htm>

TGA

- *Therapeutic Goods Act 1989 (Cth)*
<http://www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/0/6504B302BFC07061CA25775200216D33?OpenDocument>
- *Therapeutic Goods Regulations, 1990 (Cth)*
<http://www.comlaw.gov.au/comlaw/Legislation/LegislativeInstrumentCompilation1.nsf/0/0D64118EA3FFDC1BCA2577CB0002C28A?OpenDocument>
- Australian Clinical Trial Handbook, 2006 <http://www.tga.gov.au/ct/cthandbook.htm>
- *Notes for guidance on good clinical practice (CMP/ ICH/135/95) Good Clinical Practice Guidelines (with TGA notes)* <http://www.tga.gov.au/docs/html/ich13595.htm>
- *Australian Guideline for Pharmacovigilance Responsibilities of Sponsors of Registered Medicines Regulated by Drug Safety and Evaluation Branch 2005*
<http://www.tga.gov.au/adr/pharmaco.htm>
- *Access to Unapproved Therapeutic Goods – clinical trials in Australia*
<http://www.tga.gov.au/docs/html/clintrials.htm>

OTHER

Code of Ethical Standards for Catholic Health and Aged Care Services, 2001
<http://www.stvincents.com.au/assets/files/pdf/CodeofEthicalStandards.pdf>