



**Early Phase Clinical Trials
Framework for NSW**

Office for Health and Medical Research

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Abbreviations

CTN	Clinical Trial Notification
CTX	Clinical Trials Exemption
EMA	European Medicines Agency
EOI	Expression of interest
FDA	US Food and Drug Administration
FIH	First-in-human
FTIP	First time in patient
GCP	Good Clinical Practice (refers to the current version of GCP)
GMP	Good Manufacturing Practice
HREC	Human Research Ethics Committees
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational medical product
LHD	Local Health District
MHRA	UK Medicines and Healthcare Products Regulatory Agency
MRI	Medical Research Institute
NHMRC	National Health and Medical Research Council
NMA	National Mutual Acceptance
OHMR	Office for Health and Medical Research
PHO	Public Health Organisation
SOP	Standard operating procedure
TGA	Therapeutic Goods Administration

Key messages

Some core elements of the Framework to be clarified are:

1. This Framework will give participants and host institutions (e.g. LHDs) assurance that early phase trials are as safe as possible, if they are conducted in sites that achieve quality recognition (along with their associated investigators). It supports good clinical governance within host institutions.
2. This Framework will to reduce the time and administrative burden in the approval of early phase trials by setting consistent timeframes and processes for both HREC and SSA approvals.
3. Existing national process that support ethics approval and clinical trial processes in Australia (e.g. NMA and CTN) will be maintained and complemented by this Framework.
4. Resources will be made available to support the implementation of the Framework.

1 Introduction

The Office for Health and Medical Research (OHMR), NSW Ministry of Health has undertaken an open consultative process to develop a Framework for the conduct of early phase clinical trials across NSW¹. The Framework addresses a government priority, identified in the Strategic Review of Health and Medical Research (2012), to develop Phase I clinical trial capability in NSW. This Framework is one component of a broader suite of initiatives to build capacity to make NSW a centre of excellence for all phases of clinical trials.

Vision: NSW is a centre of excellence that provides a high quality and efficient environment to conduct early phase clinical trials with the ultimate aim of improving health outcomes for NSW residents.

The **guiding principles** that underpin this Framework are:

- Ensuring that early phase trials are as safe as possible for all people in NSW participating in them;
- Reducing the administrative burden in the approval and conduct of early phase trials;
- Supporting and enabling opportunities for residents and the research community across the state to engage in national and international early phase trials;
- Ensuring alignment with best practice internationally and nationally; and
- Strengthening the capability in NSW to become a centre of excellence for early phase trials.

¹ <http://www.health.nsw.gov.au/ohmr/Pages/early-phase-clinical-trials.aspx>

This Framework has been developed in response to key issues identified by stakeholders² that include:

- The lack of current, clear and consistent guidance on how to approve early phase trials to commence and monitor their conduct in NSW (or Australia). This is in contrast to the clear guidance and processes that available in Europe, the UK and USA.
- The changing definition and context of Phase I and early Phase trials, and the resulting requirement to review the relevant NSW Health policy, some of which has been in place for 10 years.
- The concern from all stakeholders about serious adverse events in Phase I trials, in the light of recent international events in the UK and France (see Appendix 2 for an overview of adverse events).

This Framework was developed between May 2016 and February 2017 through wide-ranging consultation. All stakeholders involved in the review and conduct of clinical trials in NSW had an opportunity to share their views (see Appendix 1 for overview of stakeholder consultation). All stakeholder groups consulted (industry, ethics committees and investigators from universities, medical research institutes and Local Health Districts) support the development of a Framework to support early phase trials, build capacity and make NSW competitive within an international clinical trials market.

This document is intended to be flexible to respond to changes in this dynamic field. The scope and definitions included within the Framework will be monitored to ensure their ongoing applicability and appropriateness.

² The issue of the timeliness of research governance reviews for all clinical trials including early Phase trials was raised multiple times in the initial consultations. This issue is being directly addressed by the OHMR's Research Ethics and Governance Reform that is underway (<http://www.health.nsw.gov.au/ethics/Pages/reform-framework.aspx>)

2 Overview of the Framework

Adverse events in Phase I trials in the UK and France³ have highlighted that errors can occur in both areas: through the approval process, if preclinical data is not sufficiently interrogated, and through the conduct of trials, in terms of rapid medical oversight, communication and other operational matters (Appendix 2). To minimise the risk of adverse events, this Framework will focus on developing a system and processes across NSW to support the approval and conduct of early Phase trials.

While not the primary focus of this Framework, a by-product of this the initiatives described in this document will be to build capacity through the systems and processes that will be implemented to support continuous quality improvement. More widely, NSW Health are undertaking a number of capacity building initiatives that will help to build capability in the review and conduct of early phase clinical trials across the state.⁴

The Framework has been designed as a platform that can be expanded for future capacity building initiatives that will enable the sharing of expertise across the state.

The criteria for the design of the Framework included:

- Issues raised by stakeholders in NSW to be addressed;
- Reduced length of time and increased predictability of the approval timeframes for early phase trials;
- Build capacity in early phase clinical trials in NSW;
- Ensure that NSW does not duplicate any existing and planned state, national and international initiatives (e.g. National Mutual Acceptance);
- Did not add additional processes that could be perceived as a barrier to the approval and conduct of early phase trials;
- Establish structures and processes for NSW so that there is assurance that the existing national and international standards are implemented, rather than creating new standards;
- Position NSW to rapidly adopt future changes in the clinical trials landscape;
- Accommodate changing definitions of early phase clinical trials, and their conduct, over time.

Figure 1 contains a summary schematic overview of the Framework that is further specified in following sections.

³ Horvath, C & Milton MN. 2009. The TeGenero Incidence and the Duff Report conclusions: A series of unfortunate events or an avoidable event? *Toxicol Pathol*, 37(3): 372-383.

Eddleson M, Cohen AF & Webb DJ. 2016. Implications of the BIA-102474-101 study for review of first-into-human clinical trials. *Br J Clin Pharmacol*, 81(4): 582-586.

⁴ See the OHMR website for more information on related initiatives:
<http://www.health.nsw.gov.au/ohmr>

Figure 1. Overview of proposed Framework to support early phase clinical trials in NSW

Goal	Early Phase Clinical Trial Framework for NSW	Benefits
<p>Rapid and high quality approval to commence early phase trials</p>	<p>NSW Health appointed specialist early phase clinical trials HRECs</p> <p>EOI open to all NHRMC Certified HRECs, up to five early phase specialised HRECs will be appointed for NSW.</p> <p>HRECs supported by OHMR for scientific review, and professional development</p> <p>Governance: OHMR, NHMRC</p>	<ul style="list-style-type: none"> • Host institutions and sponsors have assurance of quality and ethical trial thereby mitigating risk • Guaranteed HREC review time (20 days) and frequent committee meetings • Consistency in what is required from applicants and decision making • Specialised review of pre-clinical data • HREC continuous improvement • Recognises National Mutual Acceptance
<p>High quality operational conduct of early phase trials</p>	<p>Voluntary quality recognition scheme for early phase clinical trial sites and investigators in NSW</p> <p>Sites/units and investigators apply for quality recognition if they published meet standards. A central office will provide coordination and support capacity building of sites/units.</p> <p>Sites/units will either receive quality recognition or be supported if they are working towards it</p> <p>Governance: OHMR, Expert Oversight Committee</p>	<ul style="list-style-type: none"> • Host institutions and sponsors have assurance of quality conduct including clinical governance thereby mitigating risk • Scheme promotes continuous improvement • Guaranteed Site Specific Authorisation review time (10 days) • Sites/units have access to common SOPs and capacity building • Investigators are appropriately qualified and/or are supported

3 Scope and Definition of Early Phase Trials

The paradigm of clinical trials is changing. The current environment of early phase trials is no longer defined by the traditional Phase I first-in-human (FIH) model. This shift has come about as a result of the public and clinicians advocating for more rapid drug development and the global increase in molecule-to-medicine research.⁵ With this shift has come a range of approaches to trial design and conduct that are tailored to the relevant disease and the therapeutic good undergoing research.

Reflecting this change, the pattern of early phase clinical trials in NSW does not typically take the form of traditionally defined FIH studies. In NSW, it is estimated that for the period 2011- 2015, four out of every five early Phase trials (up to but not including Phase II) were conducted in patient populations. While it is acknowledged that this number will shift with the launch of a dedicated Phase I clinical trial unit in NSW, this local data reflects the changing definition and design of Phase I clinical trials and early phase trials.

Increased clarity in the scope and definition of the range of terms used to describe early phase trials will assist in developing a shared understanding of the range of early phase trials that are now coming through the NSW system and are covered by this Framework. Furthermore, defining the range of trial types that come under the banner of 'early phase' allows for a clear articulation of what is within the scope of this Framework.

In keeping with international trends, including the UK Medicines and Healthcare Products Regulatory Agency (MHRA)⁶ and European Medicines Agency (EMA)⁷, **the Framework will encompass a broad definition that includes all variants of early phase trials up to, but not including, Phase II.** This will ensure that definitions are in keeping with international norms and the changing context of early phase trials.

This Framework will encompass the scope and definitions of studies noted below, that draw on nationally and internationally accepted definitions.

3.1 Scope

The Framework will cover all early phase trials involving products which are defined as therapeutic goods in the National Health Act including medicines, medical devices of all classes, blood and blood products. Emerging technologies, such as cell therapies are included. The following instances are out of scope.

- Individual patient use (Compassionate use of medicine). Using therapeutic agents in these circumstances is governed by Clinical Governance within the hospital and

⁵ Prowell TM, Theoret MR & Pazdur R. 2016, Seamless oncology-drug development. *NEJM*, 374(21): 2001-3.

⁶

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/473579/Phase_I_Accreditation_Scheme.pdf Accessed 9 August 2016.

⁷

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500210825.pdf Accessed 9 August 2016.

Local Health District (LHD) most commonly this will be a Drugs and Therapeutic Committee within the hospital or LHD.

- Trials where the intervention is not a therapeutic goods as defined in the National Health Act (e.g. surgery, allied health physical therapies).

The Framework focuses on supporting Human Research Ethics Committees (HRECs) and investigators involved in the review and conduct of clinical trials, respectively. While the role of Sponsors is touched on, it is not a focus of this Framework.

The issue of the timeliness of research governance reviews for all clinical trials including early Phase trials was raised multiple times in the initial consultations. This issue is being addressed by the OHMR's Research Ethics and Governance Reform that is underway.⁸

3.2 Definition of early phase trials – investigational medicines, blood and blood products

The Framework will encompass a broad definition that includes all variants of early phase trials up to, but not including, Phase II trials. The definitions below from the FDA, NHMRC and MHRA are indicative of what will be covered. This will evolve and be refined as the Framework is implemented, based on the early phase trial work in NSW.

Due to the broad scope of trials included in this set of definitions, it is anticipated that the Framework will apply to a diverse and heterogeneous set of trials. Implementation of the Framework will need to consider the differences in the operating procedures between trials being conducted in healthy volunteers and those being conducted in patients with advanced disease (particularly cancer).

Phase 0: An exploratory investigational new drug study and also known as a “microdosing” study. Exploratory trials to establish whether the agent behaves in humans as was expected from preclinical animal studies, to gather preliminary data on pharmacodynamics or pharmacokinetics, to select promising lead candidates, or to explore bio-distribution characteristics. Phase 0 studies do not replace formal Phase I drug safety testing and do not offer any possibility of patient benefit. They are intended to speed drug development as part of the US Food and Drug Administration (FDA) Critical Path Initiative by quickly weeding out ineffective drugs early in the development process. (No therapeutic or diagnostic intent.)⁹

Phase I: Phase I studies involve the first administration of the medicine to humans. Medicines are usually given to small numbers of healthy volunteers, but sometimes to people affected by the disease the medicine is intended to treat. The purpose may be to determine safety, pharmacokinetics, pharmacological activity, side effects, preferred routes

⁸ <http://www.health.nsw.gov.au/ethics/Pages/reform-framework.aspx>

⁹ US Food and Drug Administration

of administration, or appropriate doses (for later studies). The studies are usually undertaken in centres equipped for specialised monitoring and a high degree of surveillance.¹⁰

Early Phase: All types of Phase I trials (including phase 1b and any other variant) using either healthy volunteers, volunteer patients and/or patients, including FIH.

First in human: Investigational medical product (IMP) administered to a human for the first time.

First time in patient: This is a subset of FIH, where it would be unethical or not possible to administer the IMP to a healthy volunteer. Therefore, the IMP is administered to a patient. It does not refer to a Phase II trial where the IMP was previously given to a healthy volunteer.

First in paediatric: The first time a medicine is used formally in a trial in a paediatric population, noting the medicine may have previously been trialled in adult populations.

Healthy volunteer: A well (generally healthy, not sick) person who agrees to participate in a clinical trial for reason other than medical purposes and receives no direct health benefit from participating.

Patient volunteer: A person who has a specific medical condition (e.g. asthma or diabetes etc.) relevant to the clinical trial who agrees to participate in a clinical trial for reasons other than medical purposes and is unlikely to receive a direct health benefit from participating.

Patient: A person being treated for a specific medical condition who has been invited or referred by the GP/consultant to participate in a clinical trial. Patients may receive a therapeutic benefit from the trial.¹¹

3.3 Definition of early phase trials – investigational medical devices

The Framework will encompass a broad definition that includes all variants of early phase trials up to, but not including, Phase II trials, the definitions below from the FDA are indicative of what will be covered. This will evolve and be refined as the Framework is implemented, based on the early phase trial work in NSW.

Early feasibility study: a limited clinical investigation of a device early in development, typically before the device design has been finalised, for a specific indication (e.g. innovative device for a new or established intended use, marketed device for a novel clinical application). It may be used to evaluate the device design concept with respect to initial clinical safety and device functionality in a small number of subjects (generally fewer than 10 initial subjects) when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from an early feasibility study may guide device modifications. An early feasibility study does not necessarily involve the first clinical use of a device.

¹⁰ NHMRC: The National Statement on Ethical Conduct in Research involving Humans 2007 (updated 2015)

¹¹ UK Medicines and Healthcare Products Regulatory Agency, 2015

First in human study (medical device): a type of study in which a device for a specific indication is evaluated for the first time in human subjects.

Traditional feasibility study: a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study. A traditional feasibility study does not necessarily need to be preceded by an early feasibility study.

Pivotal study: a clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects. It may or may not be preceded by an early and/or a traditional feasibility study.¹²

3.4 Case study example of out of scope clinical trials

The definition of 'early phase' in the context of this Framework is not intended to include the administration for the first time of a medicine registered for a disease(s) to patients with a different disease provided, if applicable, the molecular target is the same and the dose is within the dose range of the registered indication(s).

For example a medicine which is registered in Australia (or by an internationally recognised regulatory authority e.g. FDA, EMA) for patients with a particular cancer overexpressing a specific molecular target may be trialled in patients with another cancer type which also overexpresses the same target, provided the dose requested is within the dose range for the registered indications. Such trials can be conducted under existing processes. If the dose requested is higher than that in the registered indication then this trial would be within the processes of this Framework.

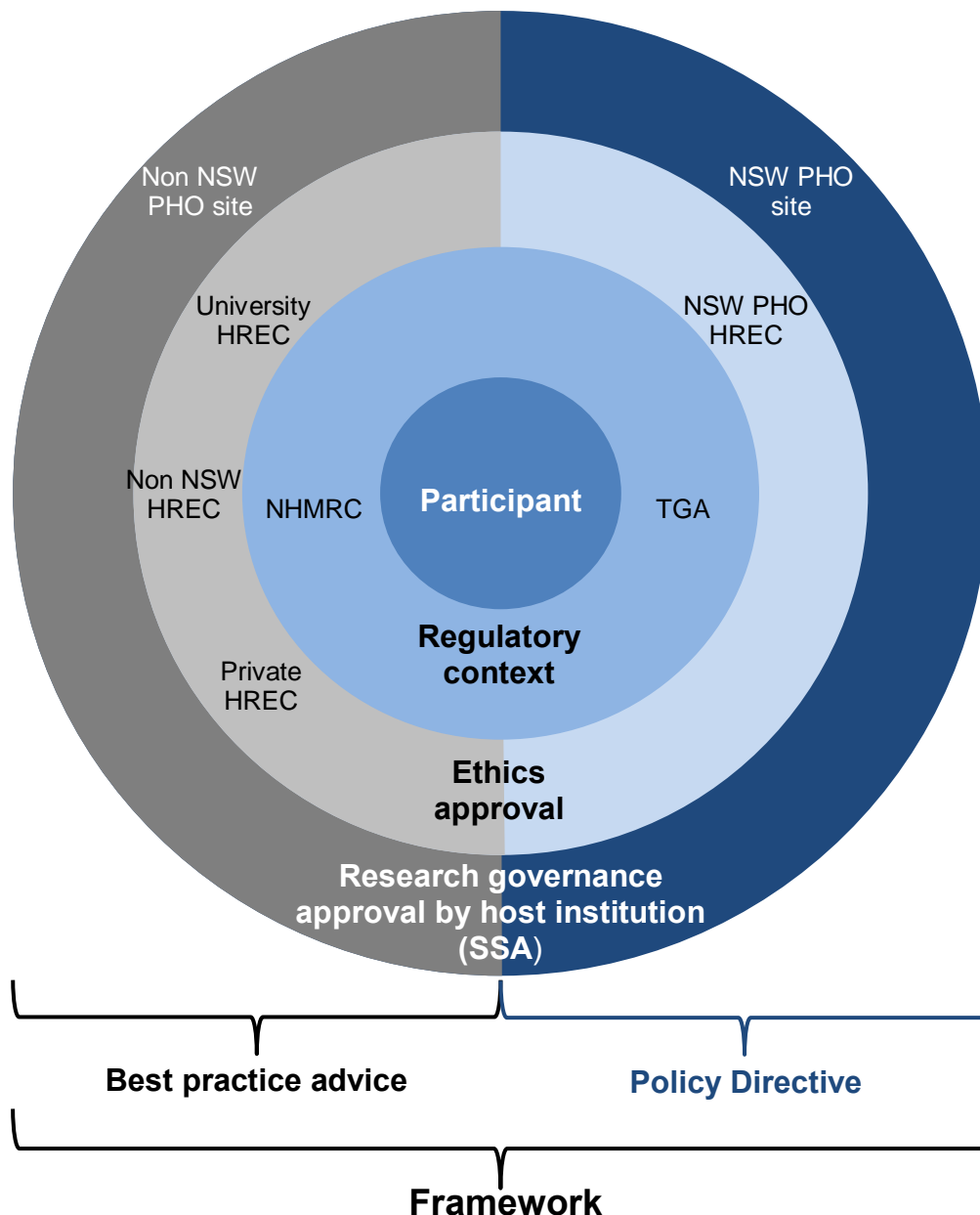
As the Framework is implemented further case studies or examples of studies that would be out of scope will be made available.

¹² US Food and Drug Administration. 2013. Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies Guidance for Industry and Food and Drug Administration Staff.

4 Overall Governance of Early Phase Trials and this Framework

This Framework encompasses what is within the purview of NSW Health and does not in any way supersede or duplicate the roles and responsibilities of other national and state bodies involved in the support, approval and regulation of clinical trials. For example, this Framework recognises National Mutual Acceptance Scheme. OHMR is responsible for the development, implementation and oversight of this Framework. Specific governance arrangements to support the components of the Framework are detailed in Sections 5.2 and 6.2. Figure 2 below outlines the governance relationships between the national government, state government, public health organisations and the private sector. Figure 2 also details how this Framework interfaces with these other arrangements.

Figure 2. Overview of clinical trial governance structures and relationships



4.1 Roles and responsibilities – early phase trials

These are briefly summarised below with a selective focus on the governance roles of these bodies over early phase trials. More exhaustive detail can be found online.¹³

Therapeutic Goods Administration – The TGA is responsible for regulating medicines and medical devices. Unapproved medicines and medical devices to be supplied in a clinical trial would require notification under the Clinical Trial Notification Scheme (CTN) or exemption through the Clinical Trial Exemption Scheme (CTX).

National Health and Medical Research Council (NHMRC) – All HRECs in Australia operate under the auspices of the NHRMC’s Australian Health Ethics Committee which oversees the registration and/or certification of HRECs that approve clinical trials to commence. The NHMRC develops the National Statement on Ethical Conduct in Human Research (2007 updated March 2014), and co-develops the Australian Code for the Responsible Conduct of Research that all trials need to be conducted in accordance with. The NHMRC also oversees the policy and implementation of initiatives support improvements to the clinical trials environment, such as the National Approach to Single Ethical Review.

Human Research Ethics Committee – Ethics committees in Australia have the primary role of assessing and approving trial proposals. HRECs conduct both a scientific and ethical review, which may be assisted on an as-needed basis by external expert advice as the committee(s) concerned see fit. All clinical trials in Australia require review and approval by an HREC. The National Statement requires that, before granting approval to a clinical trial, an HREC must be satisfied that the protocol conforms with:

- The National Statement on Ethical Conduct in Human Research;
- The World Medical Association Declaration of Helsinki;
- The International Committee on Harmonisation Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95);
- The ISO 14155 Clinical Investigation of Medical Devices and the requirements of the Therapeutic Goods Administration (TGA); and
- Any requirements of relevant Commonwealth or state/territory laws.

Sponsor – A clinical trial sponsor must meet all regulatory requirements of the TGA such as Good Manufacturing Practice (GMP), CTN and CTX, and notify the TGA of any serious and unexpected adverse drug reactions that occur during the trial and other adverse reactions/events on request. The sponsor is also responsible for establishing legal and financial agreements between the sponsor and participating institutions/organisations. These should address issues such as indemnity of the parties involved in the trial and compensation and treatment of trial participants in the case of injury or death. The general

¹³ <https://www.australianclinicaltrials.gov.au/researchers/research-principles-and-guidelines>
<https://www.nhmrc.gov.au/research/clinical-trials/australian-clinical-trials-environment>

responsibilities of sponsors of clinical trials are set out in Section 5 of the CPMP/ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) these include:

- Ensuring Quality Assurance and Quality Control systems are in place to ensure trials are conducted, and data is gathered and subsequently reported, in compliance with GCP, the trial protocol and any TGA requirements;
- Ensuring medical expertise is on hand for trial-related medical queries or patient care;
- Selecting the appropriate investigator(s) and institution(s) to conduct and complete the trial according to GCP standards; and
- Ensuring the confirmation of endorsement from the relevant HREC(s) and notification of the approval to the TGA.

The responsibilities of a sponsor in the conduct of a clinical trial are clearly identified in the Australian Clinical Trials Handbook.¹⁴

Clinical trial investigators - must obtain ethics approval for their research, notify the approving HREC and sponsor of any adverse reactions/events or changes in protocol and coordinate the conduct of the research across multiple sites if applicable. In addition, the investigator must provide appropriate and timely medical care to trial participants that is necessary as a result of any adverse events experienced during or following the trial, that are related to the trial. They must ensure that the trial is conducted in accordance with:

- The National Statement on Ethical Conduct in Human Research;
- Australian Code for the Responsible Conduct of Research;
- CPMP/ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95);
- Applicable state and territory guidelines; and
- ISO 14155:2011 Medical devices (if applicable).

Institution where the trial is being conducted – Early phase trials usually take place in hospitals or other health sector organisations that are run by State and Territory Governments or by private institutions, such as commercial specialist Phase I units. These institutions are ultimately responsible for deciding whether clinical trials take place on their premises¹⁵.

NSW Health – NSW Health develops Policy Directives to support research within Public Health Organisation (PHOs).

4.2 Governance support through linkages between NSW Health and the universities, MRIs and the private sector

There was strong consensus from all stakeholder groups that the Framework needs to support and apply to all sectors. However, Ministry of Health Policy Directives mandate

¹⁴ Therapeutic Goods Administration. Australian Clinical Trials Handbook, March 2006.

¹⁵ Note that decision making processes for sites conducting trials is out of the scope of this Framework

policy and operations to PHOs only, and does not apply to non-PHO organisations such as private health, universities and MRIs.

To support non-PHOs and to ensure the Framework will provide value to these organisations, the Ministry of Health has actively engaged non-PHO stakeholders in the process to the design of the Framework (Appendix 1). The Ministry of Health encourages non-PHO organisations to fully participate in this Framework and adopt the Framework initiatives that represent best practice where possible. This Framework has been designed so that its benefits can be equally realised across all sectors within NSW. For example:

- Any HREC irrespective of whether it is based within a PHO or non-PHO across Australia is eligible to apply to become a NSW Health appointed specialist early phase trial HREC.
- Any early phase trial, irrespective of whether it is conducted within a PHO and/or non-PHO, is able to submit its application for approval to a NSW Health appointed specialist HREC. The benefit of using a NSW Health appointed specialist HREC is that the process of approval will be efficient and of the highest standard. This will mean investigators and sponsors will receive a rapid response to their applications and host institutions will have assurance of the quality and ethics of the trial from an expert specialised HREC, thereby mitigating institutional risk.
- The voluntary quality recognition scheme for early phase sites and units is open to all sites and units across NSW, irrespective of whether their primary institution is a PHO or not. The benefits of being a unit/site that is recognised is that it can take part in quality improvement activities and market itself as a quality site/unit to sponsors and international regulators. Host institutions with sites/units within the recognition scheme will have assurance of the quality of the conduct of the trial including clinical governance, thereby mitigating institutional risk.

Governance arrangements with non-PHOs will evolve over time. Established cross-sector linkages and structures can be utilised to facilitate this Framework being applied to non-PHOs, and to ensure the benefits are shared across all sectors. Existing structures that may be utilised to implement and promote the Framework include:

- NSW Research Hubs that coordinate the research efforts of geographically proximate MRIs, LHDs, universities and community-orientated research in primary practice, established by OHMR in 2014. Through the Hubs this Framework can be communicated and promoted to non-PHO members so they can take full advantage of its benefits.
- Recurring forums between OHMR and University Deputy Vice-Chancellors of Research.
- Recurring forums and existing agreements between OHMR and MRIs.

5 Approval to commence early phase trials – NSW Health appointed specialist early phase clinical trials HRECs

5.1 Rationale, purpose and overview

Consultation with representative HREC Chairs in NSW revealed that committees often had difficulty in reviewing early phase trials for approval, particularly if trials were complex and required a depth of scientific expertise not common to most HRECs. The assumption is that when an HREC approves a study it has also considered whether the site(s) at which the study will be conducted can ensure conduct in accordance with GCP, including adequate human subject protection.

Through consultation it became clear that the status quo does not adequately support HRECs to approve early phase trials. Some issues identified were:

- State or national policy does not provide guidance on the conduct of risk assessment for early phase trials by HRECs;
- State or national policies do not require HRECs to have the full suite of appropriate scientific skills to review early phase;
- The scientific specialisation required to review early phase trials is not readily available; and
- NSW Health guidance for ethical approval including scientific review of clinical trials does not apply to private institutions.

To address these issues, it is proposed that NSW Health, through an Expression of Interest (EOI) process, appoints up to five specialist early phase HRECs drawn from all NHMRC Certified private and public HRECs in Australia to review early phase clinical trials in NSW. The number of appointed HRECs will be dependent on both the workload and the availability of appropriate expertise. The Ministry of Health will mandate the use of these appointed specialist HRECs for the review of early phase trials in NSW PHOs and will actively encourage non-PHOs within NSW to use these HRECs where appropriate.

The Framework has been designed to integrate with current schemes that streamline the approval process for clinical trials across Australia. The TGA's CTN scheme and the National Mutual Acceptance (NMA) scheme will continue to operate as they currently do, and will be complemented by the Framework.

One of Australia's competitive advantages is the CTN scheme. This model allows for the CTN scheme to be retained and utilised as the primary mechanism for clinical trial approval in NSW. Further, the scheme will provide additional support for decision making on referral to the CTX scheme, developed with input from the sector, improving consistency and reducing duplication of review.

This model allows for the continued acceptance of ethical approval from interstate HRECs under the NMA scheme. The NMA scheme allows multi-site early phase trials to commence in NSW having been reviewed by an NHMRC Certified HREC within VIC, QLD, or SA, meaning a specialist Phase I review would not be required for multicentre studies, where the

lead site is outside of NSW. The interstate-HREC must be certified under the NHMRC National Certification Scheme and also be a Certified Reviewing HREC under the NMA scheme.

There may be instances where a NSW appointed specialist committee is not recognised under the NMA scheme, for example an appointed private ethics review provider. In this instance they will only be able to accept applications for NSW-only early phase sites and their review will not be recognised by other states. Applications will be triaged by the research ethics information system to ensure there is no confusion as to which different trial types any committee is able to review.

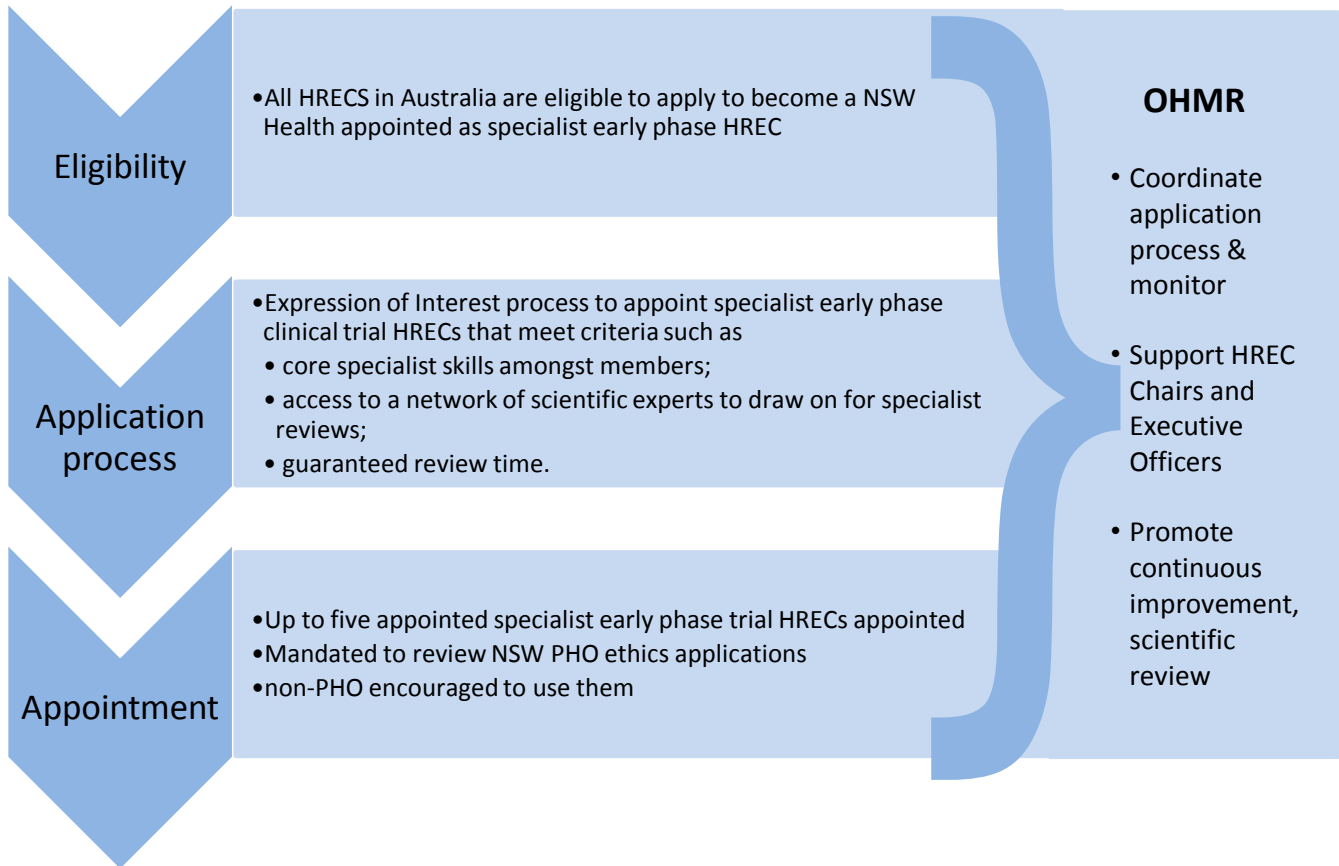
Appointed specialist committees will continue with the usual business, and in addition to that be appointed to consider the ethical approval of early phase trials in NSW.

Appointed specialist committees will receive additional support from OHMR if the committee is within a University or LHD, including:

- initial funds to support the development of the capacity to review early phase trials (for public entities in NSW)
- funds to pay for additional scientific review as required with HRECs drawing on their own networks of experts and networks that OHMR will comply for consideration (for all public entities); and
- ongoing funds to support continuous professional development, the rapid turnaround time of reviews (for public entities in NSW).

See Figure 3 for an overview of the scheme and Appendix 3 for a practical flowchart detailing the approval process from an applicant's perspective.

Figure 3. Overview of the NSW Health appointed specialist early phase clinical trials HRECs scheme



5.2 Governance and management

Role and responsibilities of OHMR

OHMR will be responsible for the overall management of the NSW Health appointed specialist early phase trials HRECs scheme. Responsibilities include:

- Develop the appointment criteria for the specialist early phase trials HRECs with an expert working group.
- Develop and manage the EOI process for appointing early phase trials specialist HRECs.
- Enter into MoUs with specialist appointed HRECs that addresses issues such as insurance.
- Develop a risk assessment tool for the appointed specialist HRECs, including clinical aspects, non-clinical aspects and quality aspects, and support for when to refer to the CTX scheme, with an external working group.
- Provide secretariat support to a 6 monthly meeting of the appointed HREC Chairs and Executive Officers.

- Monitor the performance of appointed specialist HRECs to ensure compliance with the criteria for being a NSW Health appointed specialist early phase trial HREC.
- Where appropriate, support quality assurance recommendations made by Chairs and Executive Officers (e.g. support training, development of proformas, etc.).
- Promote the usage of the appointed specialist HRECs and negotiate their use with organisations other than NSW PHOs.
- Monitor timeliness, resources and other performance of the appointed HRECs to review number of committees and resources required.
- Support appointed specialist HRECs with a state-wide panel of ex officio members with appropriate expertise, to address state-wide capability issues.

Roles and responsibilities of appointed specialist HREC Chairs and Executive Officers

As a support and quality assurance measure, the Chair (or representative Chair of an organisation with multiple committees) and EO of the appointed specialist HRECs will meet six-monthly to discuss issues with reviewing early phase trials, feedback from scientific experts, discuss changes in the nature of trials and how they can be addressed in reviews, and any other matter of common concern. This meeting could also serve as a forum to promote consistency in decision making. OHMR will provide the secretariat for these meetings.

Role and responsibilities of the appointed specialist HRECs

- Provide safe and high quality review of all applications within 20 working days (defined by days 'on the clock' from submission closing date to initial review decision) and all amendments within 10 working days.
- Invite input during the review process from a delegate of the Chief Executive(s) of all organisations hosting trial sites to be received by the date of the HREC meeting.
- Provide data to OHMR on performance as required.
- Enter into an MoU with OHMR
- All other roles and responsibilities in accordance with the National Statement and NHMRC certification (e.g. having consumer representation on the HREC).

Roles and responsibilities of NSW PHOs

- Accept the ethical review of any specialist HREC that is appointed by NSW Health to review early phase trials under this scheme.
- To accept the review of any interstate NHMRC Certified HREC if the trial is under the NMA scheme.

Roles and responsibilities of institutions or other entities hosting the certified HRECs

- Approve the application for the HREC to be appointed by NSW Health to review early phase trials under this scheme.
- Standard roles and responsibilities that they currently have.

5.3 Eligibility criteria

- All private and public HRECs or organisations providing ethical review services within Australia are eligible to apply to be appointed by NSW Health as a specialist HREC to assess early phase trials conducted within NSW.
- HRECs applying must be certified under the NHMRC National Certification Scheme.
- PHO HRECs within NMA participating jurisdictions must be a Certified Reviewing HREC under the NMA scheme.¹⁶

5.4 HREC criteria to be appointed as a specialist committee by NSW Health to approve early phase trials

Appointed committees will be selected through an EOI process. Committees will be appointed for three years, then they will need to reapply. Applications for EOIs will open every three years to coincide with renewal dates.

Appointment requirements for these committees will be developed by OHMR with a working group of stakeholders, including the NHMRC, to ensure harmonisation with other relevant initiatives. Some flexibility will be built into the criteria so that HRECs can be supported to meet specific criteria if they have an interest in being appointed. Appointment requirements may include:

- Required committee composition, including access to all the relevant scientific specialities required to review pre-clinical data and/or an appropriately constituted scientific review committee. Relevant scientific specialities will be specified.
- Mechanisms in place for rigorous scientific review of pre-clinical data in keeping with international guidance.
- Access to a wide range of scientific experts to draw upon.
- Ensure that appropriate oversight of dose escalation has been put in place by investigator(s), sponsor and safety committees (where applicable).
- Use of a risk assessment tool that will be developed by OHMR that would include support for when to refer to the CTX scheme.
- Adherence to designated benchmarks for review times.
- Ensure that appropriate mechanisms are in place to monitor units/sites in meeting and implementing GCP, GMP and other standards for early phase sites (unless sites/units have quality recognition, see Section 6).
- Ensure that appropriate mechanisms are in place for audit of approved trials.
- Nomination of further specialisation of the Committee in a specific area of early phase clinical trials e.g. paediatric or medical devices.
- Their host institution is willing to sign MoU with OHMR.

5.5 Selection process

There will be three-step application and appointment process for HRECs:

¹⁶ This applies only to PHO HRECs in Queensland, South Australia, and Victoria

1. HRECs complete and submit an application form and this will involve a self-assessment against a set of clear and well publicised criteria, along with any associated documents to OHMR. The application needs to be approved by the CEO or the entity hosting the HREC.
2. OHMR assesses the applications and may invite HREC Chairs and their institution's CE, or a delegate, for an interview.
3. OHMR makes a recommendation to the Chief Health Officer about the appointment status of the application. The appointment will be for three years and the HREC will need to reapply if they wish to be reconsidered for reappointment

5.6 Ongoing monitoring and management

HRECs will be required to provide annual reporting to OHMR against the certification criteria for the scheme, including review times. OHMR will reserve the right to withdraw the appointment of an HREC if it ceases to comply with the certification criteria.

OHMR may also conduct a user satisfaction survey of sponsors and investigators who have submitted their applications to an appointed specialist HREC.

5.7 Update NSW Health Policy Directives

NSW Health Policy Directives will be updated to mandate the use of appointed specialist HRECs under this scheme for the approval of early phase clinical trials in NSW Health PHOs.

5.8 Benefits

Benefits for investigators will be:

- Predictable and timely ethical review of early phase trial applications.
- Consistency in what is required from applicants and HREC decision making
- Rotating schedule of appointed specialist HREC meeting dates, gives more opportunities to submit applications per month, thereby making approval process more rapid.
- Having more than one expert committee appointed will enable investigators to have multiple options for committees to submit their applications.
- Access to committees whose recommendations are applicable throughout the state.

Benefits for appointed specialist HRECs will be:

- Committees could be part of a continuous improvement processes to be updated when international guidance is updated.
- Continuous improvement and development of consistency of practice through 6 monthly meeting of the appointed HREC Chairs and Executive Officers
- Specialist HRECs appointed in NSW would be well positioned to apply for any national scheme should it eventuate.

Benefits for Sponsors will be:

-
- Predictable and timely ethical review of early phase trial applications.
 - Consistency in what is required from applicants and HREC decision making
 - Rotating schedule of appointed specialist HREC meeting dates, gives more opportunities to submit applications per month, thereby making approval process more rapid
 - Access to committees whose recommendations are applicable throughout the state.

Benefits for Host Institutions of HRECs and where trials will be conducted (LHDs, universities and MRIs) are:

- Assurance that all risks associated with the approval of early phase trials would be mitigated as much as possible through a specialist review.

5.9 Potential future developments

This scheme has been designed so that it can evolve and expand over time to encompass wider functions and scope. In the initial foundational years, this specialist appointment scheme will test a proof of concept with a narrow focus on early phase trials in NSW. Over time this could be expanded cover to all phases of clinical trials, or to increase the number of appointed HRECs as required.

6 Conduct of early phase trials – voluntary quality recognition scheme for early phase clinical trial sites in NSW

6.1 Rationale, purpose and overview

In NSW, early phase trials are currently mainly sponsored by pharmaceutical companies who tend to work with Contract Research Organisations using GCP standard protocols.¹⁷ However, there is a significant minority of early trials that are not sponsored by experienced and established pharmaceutical companies which suggests that there may be significant variation in the way early phase trials are conducted in NSW. While international guidance covering quality operations of early phase clinical trials exist, Australia does not have clear and specific guidance details about the operational conduct of early phase trials.

A quality improvement scheme for sites undertaking early phase clinical trials in NSW will be established and be modelled on the UK's MHRA Phase I voluntary accreditation scheme of early phase units/sites. Advice received suggests that the MHRA scheme in the UK is well received by the sector because it is rigorous, flexible, supports capacity building and not burdensome. The main motivation for UK units to become accredited is the prestige and desire to provide, and be recognised for providing, best practice. In the initial stages of the UK scheme being established, the MHRA worked closely with clinical trials sites/units to build capacity so that they could work towards becoming accredited. Examples of the most common areas where capacity needed to be built were:¹⁸

- Issues with dose escalation;
- Incorrect dosing of subjects;
- No formal procedure for risk assessment and management;
- Failure to adequately document and demonstrate risk mitigation/management;
- Failure to update risk mitigation and management based on new information; and
- Emergency scenarios not adequate.

It is likely that these issues will be present in NSW early phase clinical trials sites/units.

In order to ensure that units and sites that conduct early phase trials operate to best practice standards in NSW, a voluntary quality recognition scheme of early phase units/sites, coordinated by a central office, will be established in NSW. The focus of the scheme will be to recognise units/sites and investigators who meet the quality criteria and build capacity within unit/sites and investigators who are working towards meeting the quality criteria. The scheme will not address the conduct of individual trials, but rather site operations, and investigator skills and experience.

¹⁷ International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Efficacy single: E6 Good clinical practice, May 1997.

<http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>

Accessed on 2 July 2016.

¹⁸ MHRA, Phase I Accreditation Scheme, Guidance document, 28 October 2015.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/473578/Phase_I_Accreditation_Guidance.pdf Accessed 1 July 2016.

Recognised units/sites will have to demonstrate that they exceed basic regulatory GCP standards by having additional procedures that pertain to early phase trials. These must demonstrate the highest standards for avoiding harm to trial subjects and for handling medical emergencies. Quality recognition will provide assurance to all involved (HRECs, Sponsors, host institutions) that these units/sites are considered to be centres of excellence.

Investigators associated with units/sites can also apply for quality recognition. Units, sites and investigators who don't meet the criteria for recognition but wish to do so will be supported to achieve quality recognition.

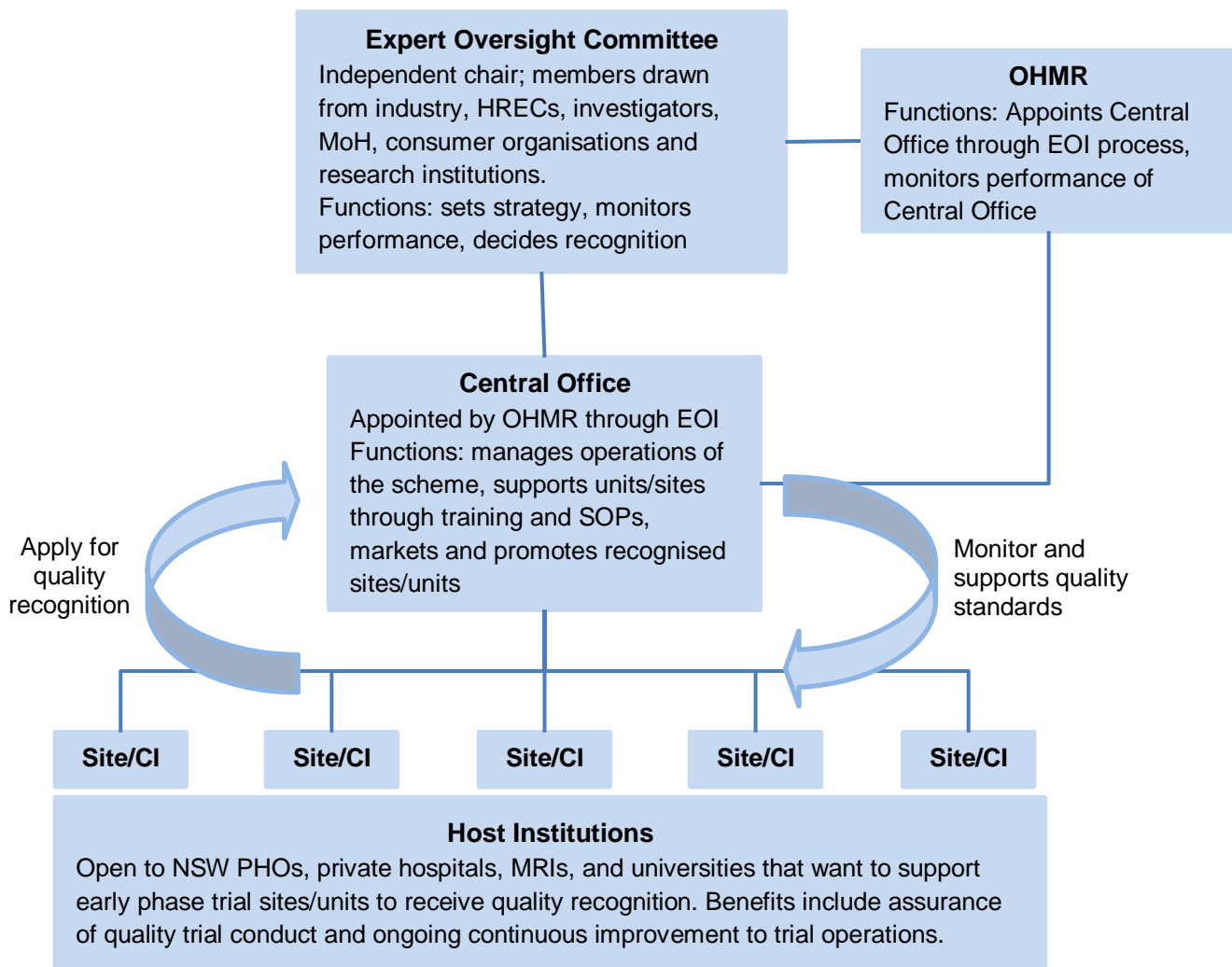
The scheme aims to ensure that the conduct of trials is as safe as possible and to create public confidence in early phase clinical trials in NSW. Specific objectives for recognised quality units and sites to:

- be supported to operate to ensure local standard operating procedures (SOPs) meet the minimum requirements of the overarching SOPs provided by OHMR;
- be supported by host institutions that agree to consistent and timely timeframes for site specific authorisation approval; and
- share expertise and training, and thereby build capacity.

This NSW voluntary recognition scheme does not duplicate other similar schemes such as the NHMRC's clinical trials ready program, because sites/units can be in either scheme. The criteria for the NHMRC's clinical trials ready has been incorporated into the indicative criteria below and extended for early phase trials.

This voluntary quality recognition scheme has been designed to accommodate possible expansion of scope over time as it becomes more established. Figure 4 below provides a visual overview of the model that will be further described in the sections that follow. Appendix 4 contains a practical flowchart detailing the application process for quality recognition process for a site/unit and indicates two pathways – full recognition and 'working towards recognition'. Appendix 5 contains a practical flowchart detailing the application process for quality recognition process for an investigator and indicates two pathways – full recognition and 'working towards recognition'.

Figure 4. Overview of the voluntary quality recognition scheme for early phase clinical trial sites in NSW



6.2 Governance and Management

Role and responsibilities of the Expert Oversight Committee

The Expert Oversight Committee will be appointed by the Chief Health Officer to advise the Director of OHMR on the development, implementation, management and improvement of the scheme. The Chair will be independent and membership could include experts drawn from:

- Clinical trials sponsors;
- Institutions that host clinical trial sites (including both public and private);
- Clinical trial investigators;
- OHMR;

- HRECs;
- Consumers;
- National/international associations/government agencies relevant to clinical trials (such as TGA, NHMRC and MHRA).

The Expert Oversight Committee may wish to draw on additional experts' opinions from time to time to assist with their decision making.

Secretariat for the Expert Oversight Committee will be provided by OHMR.

Role and responsibilities of OHMR

OHMR will be responsible for the overall management of this scheme and fulfil the following functions:

- Develop terms of reference for the Expert Oversight Committee and manage the call for EOIs for membership.
- Provide secretariat support to the Expert Oversight Committee.
- Develop the request for tender for the central office and manage the process to appoint an entity to act as the central office.
- Manage the contract and performance of the central office.
- Ensure harmonisation of the scheme with other state, national and international initiatives

Role and responsibilities of the central office

The central office will manage the quality recognition scheme and fulfil the following functions:

- Finalise common SOPs for early phase units and common SOPs for other sites with a working group drawing on existing SOPs (e.g. from Scientia, LHDs, MHRA).
- Finalise the criteria for quality recognition with a working group and the Expert Oversight Committee.
- Develop and manage the application process for sites/units to receive quality recognition.
- Develop and manage the application process for investigators to receive quality recognition.
- Conduct or outsource quality recognition reviews of the sites/units.
- Provide advice to the Expert Oversight Committee on the recommended recognition status of applications.
- Develop protocols and procedures for the operation of the scheme drawing on existing materials (e.g. MHRA).
- Create a culture of continuous improvement processes across all recognised sites/units to assist in the rapid uptake of any updates in international guidance.
- Provide reports to the Expert Oversight Committee and OHMR on performance.
- Support units/sites who wish to be recognised to meet the criteria for quality recognition.

- Provide support to recognised units/sites with ethics applications through pre-review of documentation prior to submission and assistance on post-submission changes
- Facilitate and support the usage of SOPs within sites/units.
- Facilitate networking amongst recognised units/sites including collaborating on best practice activities.
- Facilitate mentoring for and building capacity within clinical trial units and sites working towards recognition.
- Facilitate mentoring for and building capacity for investigators working towards recognition.
- Conduct ongoing audit of sites for continuous improvement of the certified sites/units to ensure they meet the quality criteria – note this is not auditing of clinical trials.
- Collect data and report on early phase clinical trial activity in NSW.
- Develop and implement a communication and marketing strategy.
- Develop and manage public information on the scheme, including criteria, application process and a public list of recognised sites and investigators.
- Support recognised sites/units to work with sponsors and determine the abilities of sponsors.
- Any other function as directed by OHMR.

Role and responsibilities of recognised units/sites

Recognised units/sites will fulfil the following functions:

- Continue to meet eligibility criteria.
- Respond to requests from the central office including an annual report.
- Meet obligations of being a recognised site/unit.

Role and responsibilities of institutions hosting quality recognition sites and units

Both public and private sector institutions may host recognised sites/units (e.g. LHDs, private hospitals, universities, MRIs). These institutions need to approve the application of a site/unit to be recognised. As part of this approval they need to ensure they will provide the following:

- Management support for clinical trials;
- Education for executives on clinical trial requirements;
- A dedicated research office/clinical trials unit;
- Secure employment for site staff with proper classifications;
- Guaranteed site specific approval review time within an agreed short timeframe (10 days).

6.3 Criteria to be recognised as quality early phase site/unit and process

The scope of the NSW scheme will encompass both standalone units and named sites within a hospital or academic setting (i.e. either a commercial organisations wards/areas or a pre-defined non-commercial clinical research facility/unit, including their named or core staff). The recognition will not cover the entire hospital and all the wards and staff, or trials performed outside the named unit.

Below are start lists of criteria to be recognised as a quality early phase unit/site, or investigator in NSW. Some flexibility will be built into the criteria so that units/sites and investigators can be supported to meet specific criteria if they have an interest in being recognised.

These criteria will be further refined by the central office and Expert Oversight Committee supported by a technical working group in the implementation phase (see Section 7). Criteria will be evidence based to ensure they have a real impact on trial safety. As the criteria are developed during the implementation phase, there may be a need to have different sets criteria dependent upon the setting and target population of the unit.

It is noted that the scheme allows for different requirements for sites conducting early phase clinical trials in healthy volunteers and those conducting trials in patient populations. This is particularly relevant to the reporting of serious adverse events where requirements will be tailored to ensure that they add value without unduly increasing administrative burden.

Indicative Criteria for Quality Recognition

For the host institution¹⁹

- Clinical research is a key strategic objective.
- Sufficient resources are in place to ensure an effective and efficient site.
- An ongoing commitment to improvement in all clinical trial processes, with a focus on quality, efficiency and transparency
- Application of national good practice governance approval processes for clinical trials and guarantee of a site specific approval review time within an agreed short timeframe of receipt of application for trials within the quality recognised Unit/Site (10 days).
- Acceptance of an ethical review from a NSW Health appointed specialist early phase trials HREC.
- Have processes in place to assess the feasibility of trial conduct and maximise the recruitment of clinical trial participants.
- Transparent costs for clinical trial activities
- Trials are carried out in a cost-effective manner.

For the unit/site

- Follows International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and EMA guidelines, and those used by other regulators as advised by the central office.
- Uses SOPs provided by the central office or locally tailored standards that are judged by the central office to provide the same standard of quality.
- Trains appropriate staff to meet ICH standards.
- Trains appropriate staff to prepare research ethics and governance applications to standards required by HRECs and LHDs.

¹⁹ These criteria are largely drawn from NHMRC Clinical Trials Ready draft criteria

- Meets minimal requirements for clinical governance at all relevant levels within the hospital (e.g. speciality, ED, ICU). These requirements could include: 24/7 access to appropriate medical support and current clinical governance arrangements in place with major tertiary centres in the event that additional care is required.
- Has processes in place to ensure that the workload of clinical trials taken on by the site is appropriately managed, to ensure that the site/unit is appropriately equipped to conduct trials it takes on and that trial capacities are appropriately managed.
- Has audit processes for clinical trials conducted at the site/unit in place.
- Has processes in place to communicate clinical trial adverse events within the host institution.
- If private sites are quality recognised then a condition is that trials are approved through either a) NSW Health appointed specialist early phase clinical trials HREC or b) ethical review from an interstate HREC through the NMA scheme.

For investigators

- Qualifications, training and experience, including relevant post-graduate qualification for early phase trials. This is to provide assurance that the investigator is able to review pre-clinical data, and where appropriate assess the pharmacology and subsequent aspects such as the proposed starting dose, dose escalation proposal/stopping criteria
- If an investigator does not have the relevant qualifications, but has extensive experience in conducting experience in early phase trials, they may apply for an exemption to the scheme requirement for qualifications.
- If an investigator wishes to be recognised, the central office can provide advice on mentoring, training and other options for the investigator who is working towards quality recognition.

Process to apply for quality recognition

There will be three-step application and quality recognition process for units/sites (see Appendix 4 for a flowchart):

1. Clinical Trial sites/units complete and submit an application involving a self-assessment against a set of clear and well publicised criteria, along with any associated documents, to the central office.
2. The central office assesses this application and completes an inspection of the site/unit to verify that all the requirements have been met.
3. The central office will make a recommendation to the Expert Oversight Committee about the recognition status of the application. The central office will advise the applicants of the decision of the Expert Oversight Committee. The certification will be for three years.

There will be two-step application and quality recognition process for investigators (see Appendix 5 for a flowchart):

1. Investigators complete and submit an application involving a self-assessment against a set of clear and well publicised criteria (e.g. see this one page application form from the MHRA),²⁰ along with any associated documents, to the central office.
2. The central office will assess this application and make a recommendation to the Expert Oversight Committee about the recognition status of the application. The central office will advise the applicants of the decision of the Expert Oversight Committee. The certification will be for three years.

6.4 Ongoing monitoring of compliance and renewal of applications

Units/sites and investigators will be required to provide annual reporting to the central office. A re-inspection will be part of the renewal process of the site/unit after three years. Investigators will need to submit a renewal application for ongoing certification after the three years.

The Expert Oversight Committee, OHMR and the central office reserve the right to inspect sites/units during the three year period to verify that all requirements are being met.

If critical findings are identified during the inspection, the central office will promptly inform the Expert Oversight Committee and OHMR, as appropriate. The legal entity which the unit/site forms part of (e.g. the LHD, private hospital or university etc.) will be notified. All HRECs that have approved trials at the unit/site will also be notified. Critical findings will be reviewed by the Expert Oversight Committee and a decision will be made as to what action should be taken, this could include suspension or revocation of the unit/site's recognition.

6.5 Benefits

For recognised quality sites/units

- State-wide coordination and support from the central office.
- Promotion of their unit/site to potential sponsors.
- In line with FDA, EMA and other international regulators.
- Ease of ethical review because the issues of ability to safely conduct a trial will be addressed through quality recognition. This could result in expedited review times for applications.
- Expedited research governance review of early phase trials done at recognised units/sites.

For HRECs

- An assurance that applicants from recognised units/sites will conduct trials to the highest operational standard.
- An assurance that applicants using recognised investigators will oversee the conduct trials to the highest operational standard.

²⁰ <https://www.gov.uk/guidance/mhra-phase-i-accreditation-scheme#principal-investigator-in-first-in-human-fih-trials>

For Sponsors

- Predictable and timely ethical review and site specific authorisation review for trials conducted in units/sites with quality recognition.
- Assurances that studies conducted at recognised units/sites will be conducted to a high operational and clinical governance oversight.
- Access to an easily accessible list of recognised sites.

For host institutions (LHDs, universities and MRIs)

- Assurances that studies conducted at their units/sites with quality recognition will be conducted to a high operational and clinical governance oversight.

For host institutions where trials will be conducted (LHDs, private health, universities and MRIs)

- Assurances that studies conducted at their units/sites with quality recognition will be conducted to a high operational and clinical governance oversight.
- Therefore all risks associated with the conduct of early phase trials would be mitigated as much as possible through quality recognition.

6.6 Potential future developments

This scheme has been designed so that it can evolve and expand over time to encompass wider functions and scope as it becomes more established. In the initial few foundational years, this early phase voluntary quality recognition scheme will test a proof of concept with a narrow focus on early phase trials in NSW. The initial phase will prioritise establishing processes and building capacity in quality processes within NSW early phase sites/ units.

Over time the scheme could expand to all phases of clinical trials and include other jurisdictions. In addition nodes of specialisation could emerge in paediatrics, oncology medical devises and other areas.

From a governance perspective it could evolve to an incorporated entity with an independent or some other self-sustaining model. In addition, the NSW quality recognition scheme could become connected to other schemes both nationally and internationally. Table 1 below contains an indicative road map of how the quality recognition scheme could evolve and be scaled up to encompass a wider scope and functions over time.

Table 1. Indicative stages of development of the NSW quality recognition scheme for early phase clinical trial sites and units

Stage of development	Focus and potential options for scale up and spread
Initial foundational period	<p><i>Governance:</i> Government initiative with an Expert Oversight Committee</p> <p><i>Focus:</i> establishing processes and building capacity in quality processes within NSW early phase sites and units. Begin to develop nodes of specialisation. Gathering data and assessing options for future.</p>

<p>Middle period - Development and trial phase</p>	<p><i>Governance:</i> Government initiative with an Expert Oversight Committee</p> <p><i>Focus:</i> Have a focus on marketing and promoting the quality recognition scheme to sponsors and international regulators. Based on stakeholder input, the evaluation of the initial period and horizon scanning develop and test new functions to see if they are feasible and will meet stakeholder needs.</p> <p><i>Scale up and spread options:</i> Test the expansion of capacity building initiatives; test sharing expertise and cross-referral of trial participants between sites; test ways to engage with trial sponsors to promote the recognised sites; consider moving from quality recognition to accreditation. In addition, consideration could be given to testing elements of models such as the Phase I unit consortia in the USA or Cancer Trials Australia.</p>
<p>Well established period</p>	<p><i>Governance:</i> Current structure or self-sustaining entity with independent board and CEO.</p> <p><i>Focus:</i> Combine the quality recognition with other elements that have been tested and are successful.</p> <p><i>Scale up and spread options:</i> Consider expanding to other phases of clinical trials and other jurisdictions.</p>

7 Next Steps – Implementation plan and evaluation

The implementation of this Framework will require engagement across multiple stakeholder groups involved in early phase clinical trials in NSW. Implementation needs to incorporate the approaches below to ensure the success, coverage and scalability of the Framework:

- **Stakeholder engagement in the governance, design and execution of the Framework.** This ensures that the Framework will be responsive to changing stakeholder needs and priorities over time. A stakeholder engagement plan will need to be developed and implemented by OHMR those with real experience in the review and conduct of early phase clinical trials across the state and nationally, across all sectors. In addition, a stakeholder engagement plan will need to be developed and implemented by the central office targeting: investigators, sponsors, regulators and units/sites.
- **Ongoing engagement with national (TGA) and international regulators (EMA, MHRA, FDA)** to ensure the quality recognition criteria will mean that trial will be accepted by these groups.
- **A focus on capacity building** across the whole early phase clinical trial sector will enable the number of quality recognition sites/units to grow over time.
- **An emphasis on data collection, performance monitoring and evaluation** to feed back into continuous improvement.
- Balancing the need for non-negotiable quality standards for early phase trial units/sites with allowing **flexibility with appropriate local tailoring to achieve standards.**

Table 2, below contains a high level action plan to implement this Framework over a two year period. Over this period, this implementation plan may have to be adjusted and a transition period for HREC changes to run in parallel with existing processes will be established.

OHMR will be primarily responsible for implementing the Framework, working in collaboration with experts from stakeholder groups. Other institutions that may be responsible for supporting OHMR in relation to specific activities are noted in Table 2, below.

OHMR will establish specialist technical working groups to develop:

- criteria for appointed specialist HRECs;
- criteria for quality recognition of units/sites and investigators;
- SOPs and international standards for quality recognition units/sites and investigators.

Table 2. Implementation plan

Activities	Responsibility
Foundational Period 0 – 6 months	
Identify a resource within OHMR to manage the implementation of this Framework	OHMR
Revise relevant NSW Health Policy Directives	OHMR
Develop a stakeholder engagement and communication plan, including development of FAQs to address common queries	OHMR
Develop specialist early phase trial HREC criteria with a technical working group	OHMR/Stakeholders
Invite EOIs for HRECs to be appointed	OHMR
Develop Terms of Reference for the Expert Oversight Committee of the quality recognition scheme	OHMR
Invite EOIs for members for the Expert Oversight Committee of the quality recognition scheme	OHMR
Appoint the chair and members of the Expert Oversight Committee	CHO
Establishment phase 6 – 12 months	
Appoint specialist early phase clinical trial the HRECs	OHMR
Promote updated NSW Health policies and the quality recognition scheme	OHMR/Stakeholders
Develop and release an EOI for the central office of the quality recognition scheme	OHMR/Expert Oversight Committee
Contract with a central office to manage the quality recognition scheme	OHMR
Develop work plan for the quality recognition scheme	Central office
Develop criteria for quality recognition of units/sites with a technical working group	Central office/ OHMR/Stakeholders
Agree the SOPs and international standards for quality recognition units/sites with a technical working group	Central office/ OHMR/Stakeholders
Early review of implementation 12 – 24 months	
Review function and number of the appointed specialist HRECs	OHMR/Stakeholders
Review work of central office & voluntary quality recognition scheme after 12 months	OHMR/Stakeholders
Review accreditation period for sites/units and investigators	OHMR/Stakeholders

After the 24 month period, ongoing monitoring of the implementation of this Framework and evaluation of its outcomes will provide useful feedback to increase its reach and value.

Evaluation and monitoring could cover:

- Implementation processes: timeliness, completeness and costs
- Indicators of acceptability: stakeholder views
- Indicators of improved processes: # appointed specialist HRECs, # applications using specialised HRECs, # time for ethics review; # time for SSA; # sites/units with quality recognition; # investigators with quality recognition;
- Indicators of safety and quality such as: changes made at sites to increase safety and quality; # sites/units with quality recognition; # investigators with quality recognition;
- Indicators of building capacity such as: # sites/units working towards quality recognition; # investigators with quality recognition;

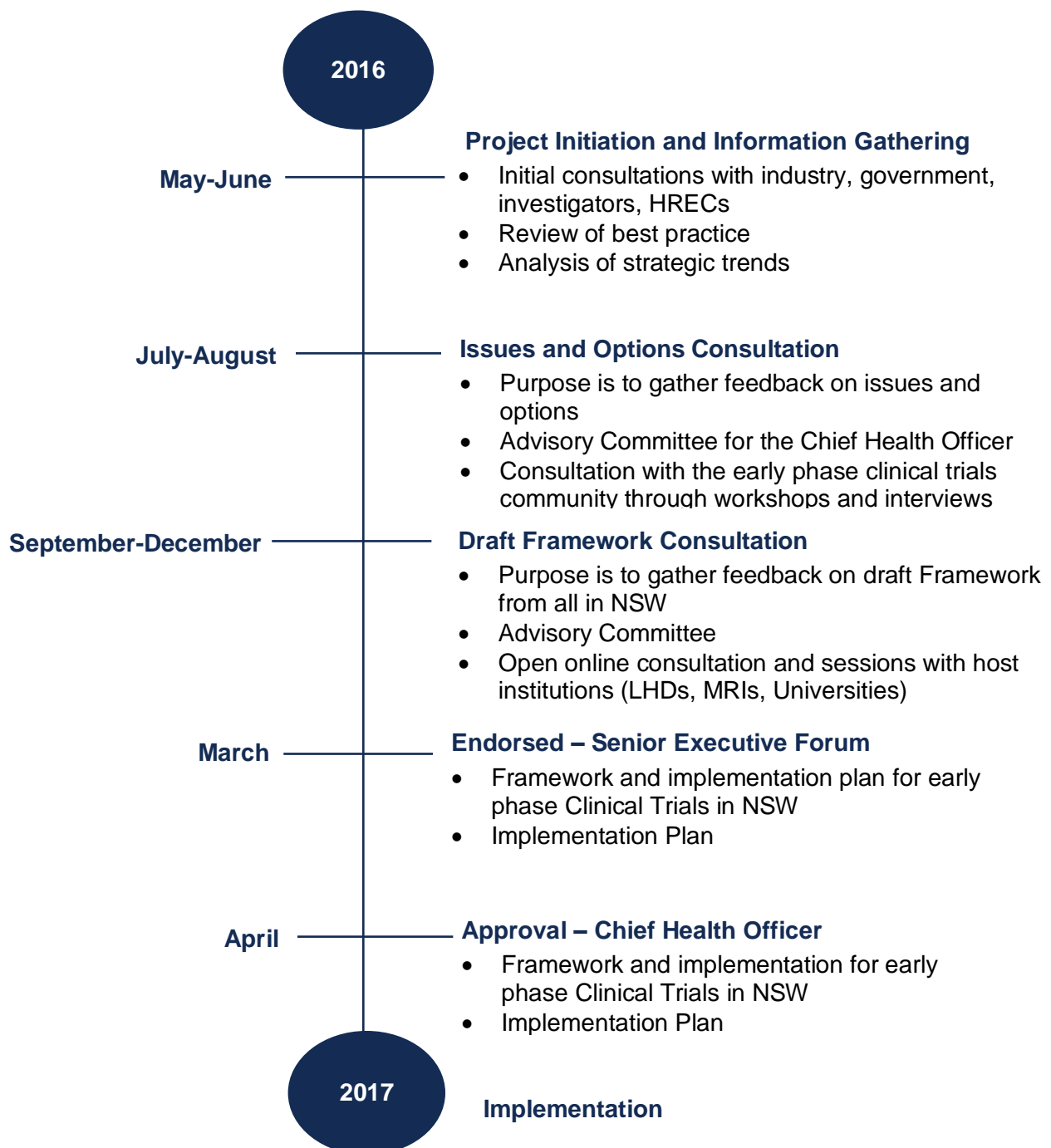
Two years is probably not a long enough time to see increased activity in early phase trials in NSW as a result of this Framework. However, we would recommend that data is collected over the first two years to examine trends, but that meaningful increases should be expected within three to five years.

Evaluation models could be:

- Internal OHMR evaluation – the evaluation is designed, conducted and recommendations made internally.
- External independent evaluation – the evaluation is designed, conducted and recommendations made externally.
- A hybrid model – whereby OHMR engages an independent expert panel to provide recommendations on the effectiveness of this Framework to achieve its vision and objectives. OHMR will collect and collate evaluation information, and an independent panel of experts will review and provide recommendations.

Whichever evaluation model is chosen stakeholders need to be engaged in the evaluation process.

Appendix 1 – Process to Develop the Framework²¹



²¹ <http://www.health.nsw.gov.au/ohmr/Pages/early-phase-clinical-trials.aspx>

Advisory Committee

Member	Position
Dr Kerry Chant	Chief Health Officer and Deputy Secretary Population and Public Health, NSW Ministry of Health
Dr Teresa Anderson	Chief Executive, Sydney LHD
Prof Warwick Britton	Head of Research, Sydney LHD
Mr Phillip Cunningham	Chief Operating Officer, St. Vincent's Centre for Applied Medical Research
Prof David Currow	Chief Cancer Officer NSW, CEO Cancer Institute NSW
Ms Lisa Emerson	Vice President, Quality , Cochlear
Dr Julie Ince-Demetriou	MedImmune Clinical Program Manager, Astra Zeneca
Prof Alison Jones	Executive Dean of the Faculty of Science, Medicine and Health
Prof Andrew McLachlan	Chair, Concord, Human Research Ethics Committee (HREC)
Prof John Simes	Senior Principal Research Fellow and Director of the NHMRC CTC
Prof Andrew Wilson	Chair of Pharmaceutical Benefits Advisory Committee Co-Director of the Menzies Centre for Health Policy, USYD
Prof Richard Day	Professor of Clinical Pharmacology, UNSW
Ms Michelle Sharkey	Chief Executive Officer, Stroke Recovery Association of NSW

Initial Consultations

Stakeholders interviewed in the initial interviews were:

- Andrew Wilson, Chair of Pharmaceutical Benefits Advisory Committee
- Lisa Nelson, Scientia Clinical Research, UNSW
- Terry Campbell, Deputy Dean, Scientia Clinical Research, UNSW
- Larry Kelly, Medical Devices and Product Quality Division, TGA
- Steve Dunlop, head pharmacovigilance and special access branch, TGA
- Samantha Robertson, Executive Director, Evidence, Advice and Governance, NHMRC
- Gordon McGurk, Director Clinical Trials, NHMRC
- Geoffrey Herkes, Chair, Northern Sydney Human Research Ethics Committee
- Andrew McLachlan, Chair, Concord, Human Research Ethics Committee
- Kylie Sproston, Chief Executive Office, Bellberry
- Connie Leggio, Director, Project Leadership Australia and New Zealand, Quintiles
- Steven Flaherty, Project Delivery Manager, Early Clinical Development, Quintiles
- James Cokayne, Office for Health and Medical Research
- Tanya Symons, Tanya Symons and Associates
- Jan Fizzell, Medical Advisor to the Chief Health Officer of NSW

- Paul Curtis, Director Governance and Assurance, NSW Clinical Excellence Commission
- Martin O’Kane, Kirsty Wydenbach, Mandy Budwal-Jagait, Mandeep Rai, Jenny Martin, UK Medicines and Healthcare Products Regulatory Agency

Workshop attendees

Three workshops were held to gather feedback on an issues and options paper²². Workshop attendees were drawn from industry, ethics committees and early phase clinical trial investigators.

Name	Organisation	Stakeholder group
Amanda Kelly Gill	George Clinical	Industry
Andrew McLachlan	Concord HREC	Ethics and Investigators
Anita Van Der Meer	Medtronic	Industry
Anthony Joshua	St Vincent’s Hospital Sydney	Investigators
Anthony Kelleher	St Vincent’s Hospital Sydney, Kirby Institute	Investigators
Barbara-Ann Adelstein	South Eastern Sydney Local Health District HREC	Ethics
Carolyn Casey	SCHN Research Governance	Ethics
Catherine Bourgeois	St Jude Medical	Industry
Catherine Morgan	Cochlear	Industry
Clement Loy	Western Sydney Local Health District HREC	Ethics
Colin Thomson	Illawarra Shoalhaven Local Health District Health and Medical HREC	Ethics
David Cook	University of Sydney	Ethics
David Fuller	INC Research	Industry
David Lloyd	Southern Star Research	Industry
David Thomas	Garvan Institute of Medical Research	Investigators
Derek Hart	Sydney Research Hub representative	Investigators
Dominic Barnes	BioPharma	Industry
Franziska Loehrer	Health-Science Alliance	Investigators
Gabrielle McKee	Clinical Network Services	Industry
Geoffrey McCowage	Westmead Hub representative	Investigators
George Faithfull	Stryker	Industry
Georgina Long	Northern Sydney Academic Health Science Alliance	Investigators
Glen Davis	University HREC	Ethics
Ian Alexander	Head, Gene Therapy Research Unit, SCHN	Investigators

²² <http://www.health.nsw.gov.au/ohmr/Documents/early-phase-clinical-trials-issues-paper.pdf>

Name	Organisation	Stakeholder group
Jacqui Everett	University of Sydney	Ethics
James Cokayne	Research Ethics and Governance unit, OHMR	Ethics
Jane Higgins	Minerva Medica	Industry
Jane Kelly	IDT CMAX	Industry
Jen Martin	Australian Society of Clinical Pharmacology and Toxicology	Investigators
Jeremy Wilson	South Western Sydney Local Health District HREC	Ethics
Karen Scanes	Parexel International	Industry
Kylie Riddell	GSK	Industry
Kylie Sproston	Bellberry	Ethics
Linda Hotong	St Vincent's Hospital HREC	Ethics
Lisa Horvath	Kinghorn Cancer Centre	Investigators
Lucia Smith	Childrens Hospital Westmead	Investigators
Luke Edington	Datapharmaustralia	Industry
Margaret Faedo	University of Sydney	Ethics
Maria Gonzalez	Melanoma Institute Australia	Investigators
Maria Mury	Northern Sydney Local Health District	Ethics
Matt Carlino	Westmead Hub representative	Investigators
Meera Agar	South West Sydney Research	Investigators
Morteza Aghmesheh	South Eastern Sydney Research Hub representative	Investigators
Nicole Denham	Research Ethics and Governance unit, OHMR	Ethics
Paul DeSouza	South West Sydney Research	Investigators
Steven Flaherty	Quintiles	Industry
Susan Alder	Minerva Medica	Industry
Suzanne Williams	Mobius Medical	Industry
Tanya Symons	Independent consultant	Ethics, investigators and industry
Trina O'Donnell	Bellberry	Ethics
Valentina Theisz	The Medical Technology Association of Australia	Industry
Valerie Carlioz	Novartis Pharmaceuticals Australia	Industry

Consultation on draft Framework

- Jane Gray, Executive Director, Partnerships, Innovation and Research, Hunter New England Local Health District and Nicole Gerrand, Manager, Research Ethics and Governance Office, Hunter New England Local Health District, (as delegates for the Michael DiRienzo, Chief Executive and Christopher Levi, Research Director)
- Danny O'Connor, Chief Executive, Western Sydney Local Health District and Stephen Leeder, Board Chair, Western Sydney Local Health District
- Suzanne Hasthorpe, Chair, National Mutual Acceptance Jurisdictional Working Group (Commonwealth Government)
- Terrie O'Brien, Ian Pieper, Erica Kneipp, Commonwealth Department of Health
- Samantha Robertson, Gordon McGurk, National Health and Medical Research Council
- Dr Jane Cook, Mounir Mina, Adrian Bootes, Claire Larter, Therapeutic Goods Administration

Submission to public consultation of draft Framework

Submissions were provided from the following organisations and individuals:

- Amgen Australia
- Bellberry Ltd
- Cancer Institute NSW
- CanTeen
- Clinical Investigation Interest Group, Medical Technology Association of Australia
- Clinical Pharmacology, School of Medicine and Public Health, University of Newcastle and Research and Innovation Division, University of Newcastle
- Clinical Research Unit, Department of Haematology, Concord Repatriation General Hospital
- CMAX Clinical Research Pty Ltd
- Dr Helen Allars, DataPharm Australia Pty Ltd
- Faculty of Health Sciences, Australian Catholic University
- Hunter New England Local Health District on behalf of Hunter New England Central Coast Mid North Coast Research Hub
- Ingham/ South Western Sydney Local Health District
- Insurance and Risk, Finance Branch, NSW Ministry of Health
- Kids Cancer Centre, Sydney Children's Hospital
- Macquarie University - Australian Institute of Health Innovation
- Medicines Australia
- National Health and Medical Research Council
- RPAH Ethics Review Committee, Sydney Local Health District
- Scientia Clinical Research Ltd
- St Vincent's Hospital Sydney Research Office
- Tanya Symons
- The Kinghorn Cancer Centre, St Vincent's Hospital Sydney

- The Sydney Children's Hospitals Network
- Therapeutic Goods Administration
- UK Medicines and Healthcare Products Regulatory Agency
- University of Technology Sydney
- Western Sydney Local Health District

Appendix 2 – Case Studies of international Phase I studies resulting in participant deaths

Below are two case studies of recent Phase I trials that had severe adverse events that provoked the international trials community to consider how Phase I trials are approved and conducted.

Northwick Park, London trial of TGN1412, England 2006

Run by Parexel; sponsored by TeGenero^{23,24}

What happened? During a first-in-man study of immunomodulatory drug, TGN1412, conducted in a private clinic, six healthy male volunteers experienced severe inflammatory reactions causing organ failure after receiving the first dose.

Why did it happen? The final report into this incident by the Expert Group on Phase One Clinical Trials, chaired by Gordon Duff, found that Parexel, the company managing the trial, had been unclear about a safe dose to start testing on humans and it should have tested the drug on one person at a time. Moreover, there was no law at the time in the UK that required consideration of safe dose for Phase I trials. It concluded that "...preclinical development studies that were performed with TGN1412 did not predict a safe dose for use in humans, even though current regulatory requirements were met."

What changes did this incident provoke? The report made 22 recommendations for pre-Phase I, "first-to-human" trials using new drugs or drugs that alter the immune system. The recommendations addressed five areas: preclinical research, drug dosing strategy, reviewing clinical trial applications for risky compounds, facilities for first-in-man clinical trials, and training for clinical investigators. In response, the UK MHRA tightened its clinical trial regulations, with initiatives including:

- New guidelines on a range of topics, including dosing protocols and training for investigators for studies of certain classes of drugs that have never before been tested in humans, including biological molecules with novel mechanisms in man, new agents that are highly species specific and new drugs directed toward immune system targets.
- Ensuring that specialised scientific committees look at quality, pre-clinical and clinical data.
- Streamlining the regulation of clinical trials and collaborating with other bodies and experts to collect as much information as possible on risk factors before a trial is authorised.

Prompted by the report, the EMA has also issued new guidelines regarding high-risk compounds²⁵.

²³ Sinha, G. 2007. Britain adopts more stringent rules for Phase I trials of high-risk compounds. *J Natl Cancer Inst*, 99(12): 915-917.

²⁴ Horvath, C & Milton MN. 2009. The TeGenero Incidence and the Duff Report conclusions: A series of unfortunate events or an avoidable event? *Toxicol Pathol*, 37(3): 372-383.

Rennes trial of BIA 10-2474, France 2016

Conducted by Biotrial, sponsored by Bial²⁶

What happened? Six healthy male volunteers were injured, one of whom subsequently died, in a private clinic after being given a Fatty Acid Amide Hydrolase FAAH inhibitor in its first study with multiple-dosing. The MRI of those injured suggested the injuries were consistent with deep-brain haemorrhage and necrosis.

Why did it happen? One participant in the multiple ascending dose cohort became ill after the 5th dose and subsequently died. Despite this incident classifying as a Serious Adverse Event, it was not recorded and the trial was not stopped. Communication of this event did not occur amongst trial staff, and as a result, seven other participants in the same multiple ascending dose received the same dose the following morning.

An interim report criticised the trial on three points:

- a) continuing the study after admission of the first patient into hospital;
- b) not informing the regulator within 24 hours of one participant being admitted to hospital; and
- c) not re-consenting the other participants after the serious adverse event.

What changes might this incident provoke? Possible changes that might arise out of this incident are that structured systematic processes for risk assessment that are now part of standard protocol in countries such as the Netherlands are applied to all trials with novel compounds, not just high risk ones; and increasing the requirements for careful monitoring of pharmacological and clinical effects during dose escalation. This approach is also taken in the UK, where expert committee review is not restricted to just high risk compounds.

EMA FIH guidelines have been updated following this incident.²⁷

²⁵

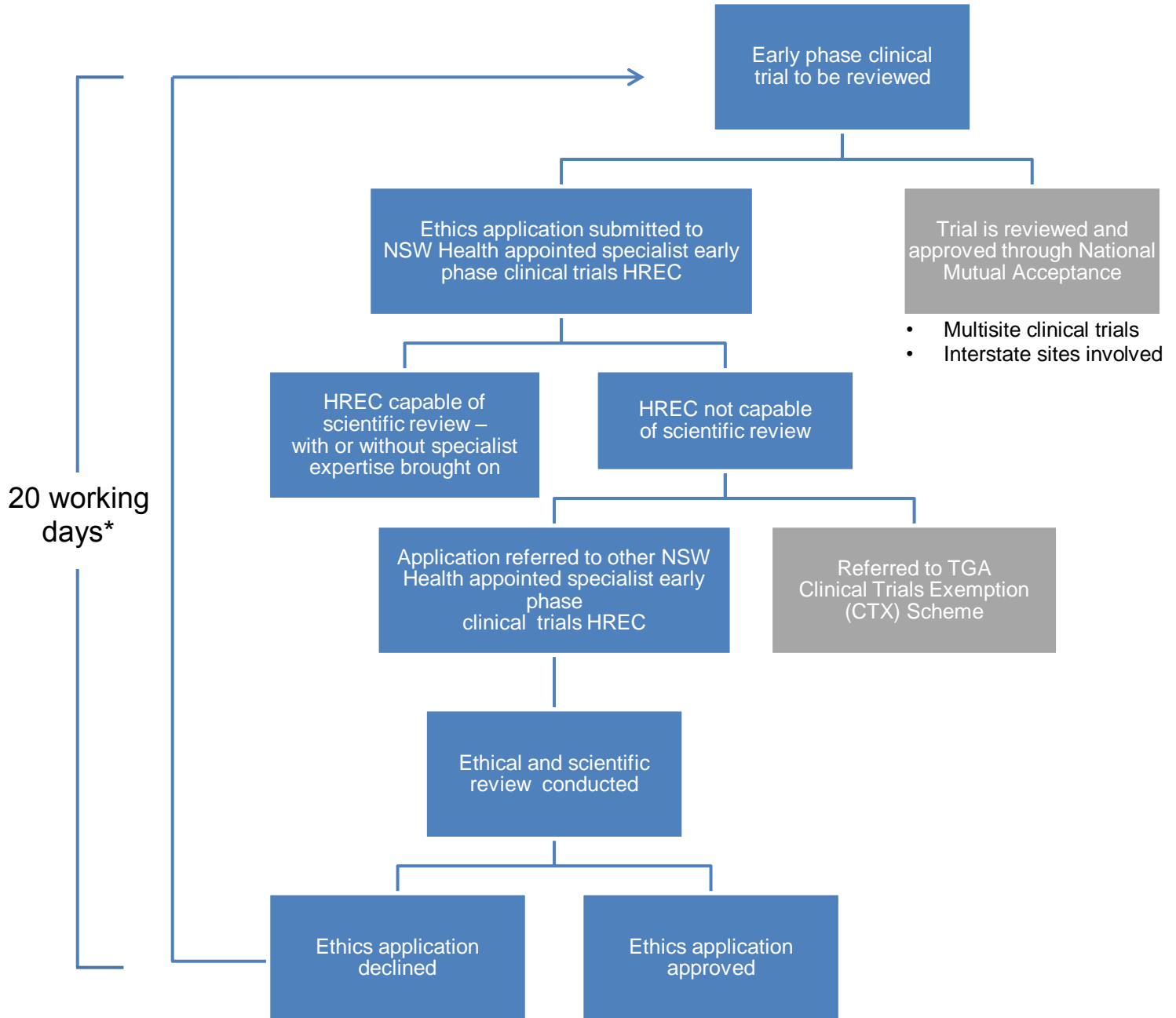
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf

²⁶ Eddleson M, Cohen AF & Webb DJ. 2016. Implications of the BIA-102474-101 study for review of first-into-human clinical trials. *Br J Clin Pharmacol*, 81(4): 582-586.

²⁷

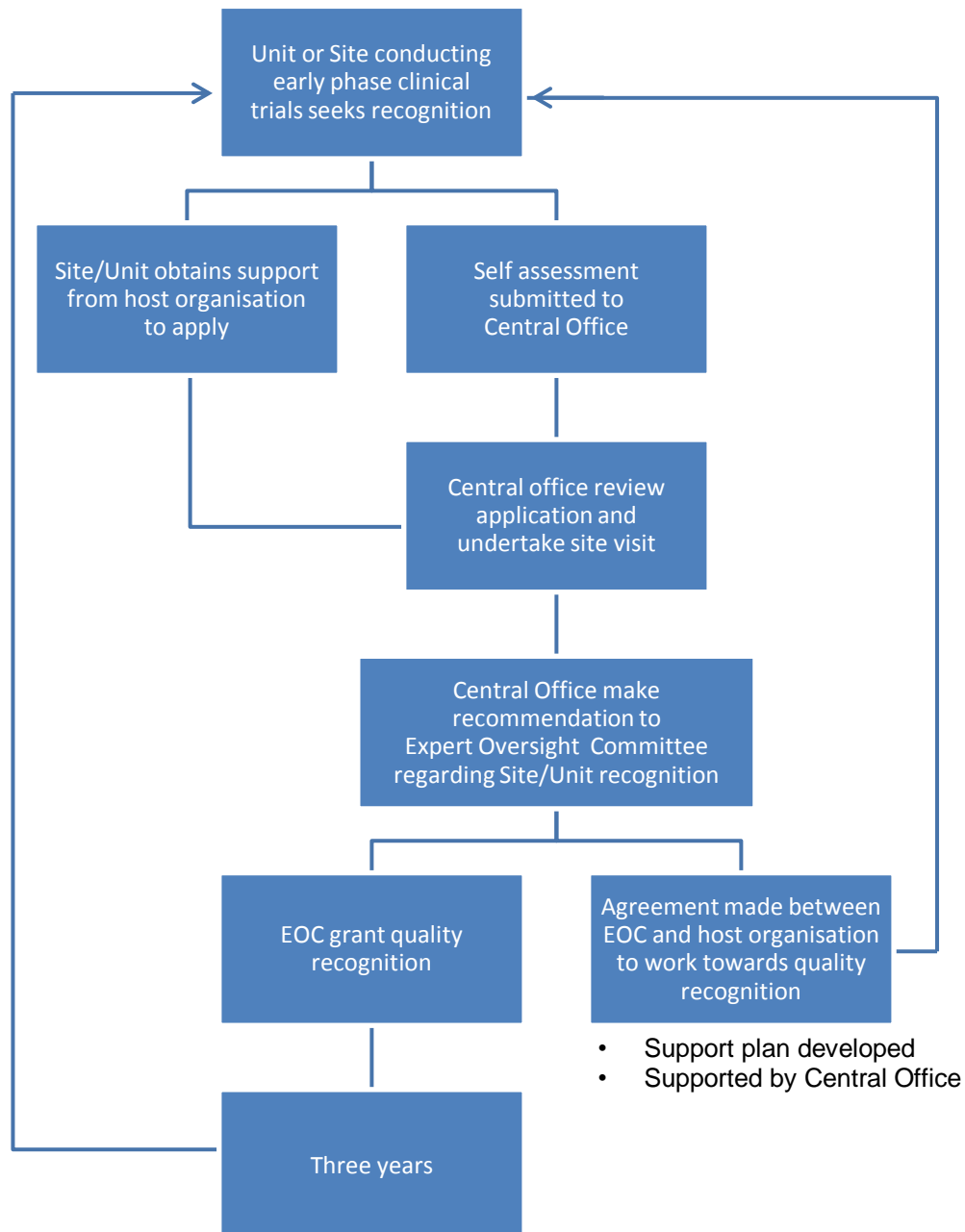
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/11/WC500216158.pdf

Appendix 3 – Ethics approval process for early phase clinical trials



* See 'Role and responsibilities of the appointed specialist HRECs' Section 5.2 for definition

Appendix 4 – Application process for quality recognition process for an early phase clinical trial site/unit



Appendix 5 – Application process for quality recognition process for an early phase clinical trial investigator

