NBMLHD Human Research Ethics Committee

Standard Operating Procedures

Updated 20th July 2018

CONTENTS

HREC 001: NSW Health HRECs

Objectives

1.1. The objectives of the HREC are to:

a) Protect the mental and physical welfare, rights, dignity and safety of participants of research;

b) Promote ethical principles in human research;

c) Review research in accordance with the *National Statement on Ethical Conduct in Human Research* (2007); and

d) Facilitate ethical research through efficient and effective review processes.

Functions

1.2. The HREC functions on behalf of the Public Health Organisation are to:

a) Provide independent oversight of human research projects;

b) Provide competent, timely review and monitoring of human research projects in respect of their ethical and scientific acceptability for as long as projects are active;

c) Determine the compliance of a human research project with the *National Statement* and grant, withhold or withdraw ethical approval; and

d) Provide advice to the Public Health Organisation on strategies to promote awareness of the ethical conduct of human research.

Accountability

1.3. The HREC is directly accountable to the Chief Executive of the Public Health Organisation under which it is constituted. The minutes of each HREC meeting are forwarded to the Chief Executive or delegate following confirmation.

1.4. The HREC provides an annual report to the Chief Executive or delegate at the end of each financial or calendar year.

1.5. The HREC brings to the attention of the Chief Executive or delegate issues of significant concern.

1.6. The HREC provides the following reports on behalf of the Public Health Organisation:

a) Australian Health Ethics Committee (AHEC) report in accordance with the requirements of the National Health and Medical Research Council (NHMRC);

b) NSW Privacy Commissioner report in accordance with the requirements of the *Health Records and Information Privacy Act 2002* (NSW).

Scope of responsibility

<u>Single-centre research applications</u>

1.7. The HREC provides ethical and scientific review of single-centre research at sites within its jurisdiction.

Multi-centre research applications

1.8. Lead HRECs provide ethical and scientific review of multi-centre research applications on behalf of the NSW public health system. A Public Health Organisation accepts ethical approval for a multi-centre research project from a suitably accredited lead HREC.

1.9. Lead HRECs have been accredited by the Director-General of NSW Health to review multi-centre research applications in one or both of the following areas:

a) Clinical trials/interventional clinical research; and/or

b) General research (including epidemiological research, population health research, health services research, clinical research of a non-interventional nature and other general categories of research).

Ethical and scientific review for external entities

1.10. The HREC reviews human research applications for external institutions/ organisations and investigators as approved by the Chief Executive.

1.11. Provision of ethical and scientific approval to an external entity is conditional upon the execution of an agreement which specifies the respective legal responsibilities and liabilities for the HREC and the external entity. Refer to Policy Directive 2008_046 *Human Research Ethics Committees: Ethical Review for External Entities*.

Role of the Chairperson

1.12. The Chairperson is responsible for the conduct of HREC business and for ensuring that the HREC reaches decisions on all matters. Where the Chairperson is unavailable the meeting will be chaired by the Deputy Chairperson if available, or by the alternate Deputy Chairperson or a HREC member with appropriate scientific and ethical knowledge in the review of research applications.

HREC Executive Committee

1.13. The HREC has an Executive Committee comprising at least the HREC Chairperson or their delegate and a member of the research office.

1.14. The HREC Executive Committee undertakes expedited review of business that does not require full HREC review, including some or all of the following:

a) Amendments to current HREC approved projects;

b) Responses to HREC queries, as approved by the full HREC for HREC Executive Committee review and approval;

c) Annual progress reports and final reports; and

d) Serious adverse events and suspected unexpected serious adverse reactions reports.

e) Any other business arising as required.

1.15. The minutes of the HREC Executive Committee are noted at the next HREC meeting.

1.16. The Chairperson has the discretion to delegate to the Executive Officer the authority to undertake review of HREC Executive Committee business that is considered administrative or within the capacity of the Executive Officer such as:

a) Amendments to Participant Information Sheets and Consent Forms that address changes requested by the HREC and require little interpretation of the ethical impact of the amendments. Changes include standard statements regarding insurance/indemnity, contact details, version control, dates, etc.;

b) Amendments to other study documents (e.g. case report forms, patient diaries) that are administrative in nature or of low ethical risk;

c) Changes to project personnel; and

d) Other issues, on a case-by-case basis, such as responses to HREC queries and annual progress reports and final reports.

HREC subcommittees

1.17. HREC subcommittees are appointed to carry out scientific or technical review of applications. The Chairperson of a subcommittee is appointed by the Chief Executive. Members of the subcommittee need not be members of the HREC, and are appointed by the subcommittee Chairperson.

1.18. The minutes of the subcommittee meetings are noted at the next HREC meeting.

Information about HRECs

1.19. Public Health Organisations ensure the following information about their HREC(s) is publicly available:

a) HREC contact details;

b) Submission closing dates for HREC meetings (and scientific/technical subcommittees if applicable);

c) HREC meeting dates;

d) The specific area of research the lead HREC is accredited to review (i.e. clinical research, general research); and

e) The sites within their jurisdiction for ethical and scientific review.

1.20. The Department of Health ensures that the name and contact details of NSW Health HRECs are publicly available on the Department's website.

1.21. Where the HREC has ceased to function, the Public Health Organisation notifies the Department of Health and the NHMRC and determines the appropriate course of action.

HREC 002: HREC composition

2.1. The composition of the HREC is in accordance with the *National Statement*. Minimum membership comprises eight members. As far as possible, men and women are represented in equal numbers and at least one-third of the members are external to the institution for which the HREC is reviewing research. The membership comprises representatives from the following categories:

a) A Chairperson with suitable experience whose other responsibilities will not impair the HREC capacity to carry out its obligations under the *National Statement*;

b) At least two members who are lay people, one man and one woman, with no affiliation with the institution or organisation and not currently involved in medical, scientific, legal or academic work;

c) At least one member with knowledge of, and current experience in, the professional care, counselling or treatment of people;

d) At least one member who performs a pastoral care role in the community, for example, an Aboriginal elder or a minister of religion;

e) At least one member who is a lawyer, where possible one who is not engaged to advise the institution for which the HREC is reviewing research; and

f) At least two members with knowledge of and current research experience that is relevant to the applications to be considered at the meetings they attend.

2.2. To ensure the HREC is equipped to address all of the relevant considerations arising from the categories of research, some or all of the above membership categories may be represented by more than one person.

2.3. No member is appointed in more than one of the membership categories. Public Health Organisations are encouraged to establish a pool of inducted members in each membership class who attend meetings as needed to meet the HREC requirements and are available to provide expertise for the research under review.

2.4. The HREC is free to consult person(s) considered by the HREC to be qualified to advise and assist in reviewing applications provided that there is no conflict of interest and an undertaking of confidentiality is given. Such person(s) are not entitled to vote on any matter.

HREC 003: Appointment of members

3.1. HREC members are recruited by direct approach, nomination or by advertisement through an open and transparent process.

3.2. Prospective members may be invited to observe a meeting of the HREC.

3.3. Prospective members are asked to provide a copy of their curriculum vitae to a selection committee comprising the Chairperson, Executive Officer and at least one other HREC member. The selection committee interviews prospective members, consults with HREC members and makes a recommendation on new appointments to the Chief Executive.

3.4. Members are appointed as individuals for their knowledge, qualities and experience and not as representatives of any organisation, group or opinion.

3.5. Membership of the HREC is made publicly available.

3.6. All members including the Chairperson, Deputy Chairperson and Chairperson of any subcommittee are appointed by the Chief Executive. The letter of appointment includes the date of appointment, length of tenure, indemnity and termination.

3.7. Upon appointment, members are provided with an orientation package and asked to sign a statement undertaking:

a) that all matters of which he/she becomes aware during the course of his/her work on the HREC will be kept confidential;

b) that any conflicts of interest, which exist or may arise during his/her tenure on the HREC will be declared; and

c) that he/she has not been subject to any criminal conviction or disciplinary action, which may prejudice his/her standing as an HREC member.

3.8. Members are appointed for a period of up to 3 years and may serve only 6 years unless otherwise approved by the Chief Executive or delegate. The Chief Executive or delegate, in consultation with the Chairperson, may implement a probationary period.

3.9. The Chairperson, Deputy Chairperson and Chairperson of any subcommittee may serve longer terms with the approval of the Chief Executive or delegate. Members are advised when their term has expired. Reappointment is by application to the Chairperson of the HREC who then makes a recommendation to the Chief Executive or delegate.

3.10. New and renewed appointments allow for continuity, development of expertise within the HREC, and regular input of fresh ideas and approaches.

3.11. Membership lapses if a member fails to attend:

a) Three consecutive meetings without reasonable excuse/apology or exceptional circumstances; and

b) At least two thirds of all scheduled HREC meetings in each year, barring exceptional circumstances.

3.12. The Chairperson notifies the member of a lapse of membership in writing. Steps are taken to fill the vacancy.

3.13. Members seeking to resign or take a leave of absence for an extended perod from the HREC are asked to give notice to the Chairperson. Steps are taken to fill the vacancy.

3.14. The appointment of any member of the HREC may be terminated if the Chief Executive or their delegate is of the opinion that:

a) It is necessary for the proper and effective functioning of the HREC;

b) The person is not a fit and proper person to serve on an HREC; or

c) The person has failed to carry out their duties as an HREC member.

3.15. Members are expected to participate in relevant specialised working groups as required.

3.16. The Chairperson is expected to be available between meetings to participate in HREC Executive Committee meetings where required.

3.17. The Public Health Organisation provides indemnity for members of the HREC for liabilities that arise as a result of the member exercising their duties in good faith. Such indemnity is provided through the NSW Treasury Managed Fund.

HREC 004: Orientation and training of members

4.1. New HREC members are provided with orientation/training as determined to be appropriate by the Public Health Organisation.

4.2. Orientation involves some or all of the following:

a) Introduction to other HREC members prior to the HREC meeting;

b) Provision of an orientation package;

c) Informal meeting with the Chairperson and Executive Officer to explain their responsibilities as an HREC member, the HREC processes and procedures;

d) 'Partnering' with another HREC member in the same category; and

e) Priority given to participate in training sessions.

4.3. Each member is:

a) expected to become familiar with the *National Statement* and consult other guidelines relevant to the review of specific research applications; and

b) encouraged to attend continuing education or professional development activities in research ethics once in each period of appointment.

HREC 005: Meeting schedules

5.1. The HREC meets on a regular basis at least every 6 weeks. The HREC holds at least 8 scheduled meetings in each year for the purposes of reviewing new applications.

5.2. Meeting dates and application closing dates are made publicly available.

5.3. Additional meetings are held where necessary to ensure that reviews are completed within a timely fashion, to discuss matters relating to the establishment or operating procedures of the HREC or for training purposes.

5.4. The schedule of HREC meetings for the calendar year commencing 1 January is ratified by the HREC before or at the last meeting of the previous year. The schedule sets out the dates, times and venues of meetings, and the closing date for submission of applications.

5.5. Scientific subcommittees issue similar schedules to their members.

HREC 006: Agenda

6.1. The Executive Officer prepares an agenda for each HREC meeting.

6.2. The meeting agenda and associated documents are circulated to HREC members at least 7 days prior to the next meeting electronically and/or as paper copies.

6.3. Documentation received after the closing date are included on the agenda and/or tabled at the meeting at the discretion of the Executive Officer and/or Chairperson.

6.4. New applications received after the closing date are not tabled at the meeting.

6.5. As a minimum, the agenda includes the following items:

a) Attendance and apologies;

b) Declarations of conflicts of interest relating to agenda items;

c) Confirmation of minutes of the previous HREC meeting;

d) Business arising since the previous meeting(s) that the HREC indicated it wished to reconsider;

e) Minutes of meetings and any issues for noting and/or approving from the HREC Executive Committee, subcommittees and external expert reviewers for example:

f) Amendments to documents or modifications to applications and research projects;

g) Annual progress reports and final reports;

h) Reports of serious adverse events and suspected unexpected serious adverse reactions;

i) New applications for review and, if applicable, the spokesperson or lead reviewer nominated by the HREC to lead the discussion on each application;

j) General business; and

k) Notification of the date, time and venue of the next scheduled meeting.

6.6. The agenda and all documentation are confidential.

HREC 007: Lead reviewers

7.1. The HREC has the discretion to appoint one or more members as lead reviewers for the HREC meeting or the subcommittee meeting for each application.

7.2. Allocation of applications to lead reviewers is made by the Executive Officer in consultation with the Chairperson, as necessary.

7.3. The lead reviewer is provided with a copy of the application and other supporting documentation which they have been allocated to review.

7.4. The specific role undertaken by the lead reviewer both at the meeting and following the meeting is at the discretion of the HREC. Local procedures are discussed and agreed by the members.

HREC 008: Attendance of the Co-ordinating Investigator

8.1. At the request of the HREC Chairperson, the Co-ordinating Investigator is invited to make formal presentation or to respond directly to requests from the HREC for further information, clarification or reassurance.

8.2. Where the Co-ordinating Investigator is unable to attend, another key investigator or collaborator is invited to attend, if appropriate. Representatives of the sponsor are not to attend the meeting in place of the Co-ordinating Investigator. Other members of the research team may attend with the Co-ordinating Investigator.

8.3. The Co-ordinating Investigator attends the meeting in person or via telephone or videoconference.

HREC 009: Quorum requirements

9.1. A quorum is required at each meeting for the HREC to reach a final decision on any agenda item. The quorum for meetings is at least one member from each of the core categories and the Chairperson/Deputy Chairperson as specified in the *National Statement* attending in person or via telephone or videoconference.

9.2. A quorum can be reached where there is less than a full attendance of the minimum membership at a meeting but if the Chairperson is satisfied "that the views of those absent who belong to the minimum membership have been received and considered", for instance through prior submission of written comments.

9.3. Where a quorum is not reached, the HREC will not commence, continue or conclude discussion with the purpose of reviewing an application. The HREC has the discretion to proceed with other business on the agenda as if it were an HREC Executive Committee meeting, provided that the Chairperson (or Deputy Chairperson or alternate Deputy Chairperson) and at least one other member is present.

9.4. Where the Executive Officer of an HREC is concerned that a forthcoming meeting will not be attended by a quorum of members the Executive Officer notifies the Chairperson and the following options are considered:

a) Postponing and re-arranging the meeting; or

b) Cancelling the meeting.

HREC 010: External expert reviewers

Use of external expert reviewers

10.1. An HREC unable to make a decision on an application or without the necessary expertise is able to seek the advice of an external expert reviewer through the NSW Health Shared Scientific Assessment Committee or through experts identified in the area by the Chairperson and/or the Executive Officer.

10.2. The Shared Scientific Assessment Committee provides independent scientific review of clinical drug trials for NSW Health HRECs that are unable to meet the provisions in Policy Directive 2007_035 *Standards for scientific review of clinical trials*.

10.3. Advice from other external expert reviewers is sought through the following procedures

a) Notification is sent to the Co-ordinating Investigator either before or following the HREC meeting explaining that a final decision will not be made on the application until advice is obtained from an expert reviewer. The letter notifies the Co-ordinating Investigator of the issues of concern to the HREC, but does not request further information or clarification. In circumstances where expert scientific opinion is sought, the Co-ordinating Investigator is given the option to identify experts to whom they object.

b) A suitable expert reviewer is identified by the Chairperson/Executive Officer or by the HREC during the meeting.

c) The Chairperson or Executive Officer initially contacts the prospective expert reviewer(s) by telephone or email to establish whether they are available to provide expert advice within the required time frame and that they have no connection with the research that might give rise to a conflict of interest. The expert reviewer is advised about confidentiality requirements.

d) The Executive Officer specifies in writing the issues of concern to the HREC and the expert advice required, and requests written advice and/or attendance (but not voting) at the HREC meeting. The Executive Officer ensures that the expert reviewer declares any conflict of interest and signs a declaration and confidentiality agreement.

10.4. A copy of the application form is provided together with any supporting documentation required by the expert reviewer. The HREC, or HREC Executive Committee or subcommittee as appropriate, considers the advice of the expert reviewer and makes an independent decision on the ethical and scientific acceptability of the application. The advice is recorded in the minutes.

HREC 011: Declaration of interest

11.1. An HREC member declares to the HREC any conflicts of interest they have in relation to an application for ethical and scientific review or any other matter for consideration at that meeting. Conflict of interest includes financial interests, personal, professional or institutional benefits or advantages that depend significantly on the research outcomes.

11.2. Declarations are made orally at the meeting prior to the matter being considered or in writing to the Chairperson prior to the meeting. The HREC determines whether the level of interest results in:

a) A substantial conflict of interest: a member is excluded from the meeting where there is a substantial conflict of interest until the HREC has concluded consideration of the matter. Being an investigator on a research project is considered to represent a substantial conflict of interest.

b) A non-substantial conflict of interest: the member has the discretion to leave during the discussion of the matter.

11.3. The minutes record declaration of interest and the decision of the HREC on the procedures to be followed.

HREC 012: Confidentiality

Confidentiality of meetings

12.1. The confidentiality of HREC proceedings is essential as:

a) Members do not sit on the HREC in a representative capacity;

b) Applications need to be discussed freely; and

c) Applications may have commercial implications.

12.2. HREC meetings are held in private and members are encouraged to raise matters of concern.

12.3. Confidentiality is addressed in two ways:

a) The HREC Terms of Reference; and

b) Members signing a statement of undertaking upon appointment.

12.4. Attendance of visitors or observers at a meeting, as appropriate and approved by the Chairperson, is conditional on the attendee signing a confidentiality agreement.

Confidentiality of applications

12.5. Applications, supporting documentation and correspondence are treated confidentially.

12.6. External expert reviewers providing advice to the HREC are asked to sign a confidentiality agreement.

12.7. HREC correspondence is addressed to the Co-ordinating Investigator and sent to the Co-ordinating Investigator or the relevant contact person identified on the application form. Correspondence is not released to the sponsor or any other parties.

12.8. Co-ordinating Investigators forward information about matters raised in the ethical review to sponsors or other parties where necessary.

HREC 013: Decision making

13.1. Members present are allowed reasonable opportunity to express relevant views on matters on the agenda.

13.2. The HREC endeavours to reach a decision concerning the ethical and scientific acceptability of a research project by unanimous agreement.

13.3. Where a unanimous decision is not reached, the matter is determined by a majority of two-thirds of members present at the meeting, provided that the majority includes at least one layperson.

13.4. Any significant minority view (i.e. 2 or more members) is noted in the minutes.

13.5. Discussions of significant issues and decisions are recorded in the minutes. Where members wish, a record of their formal dissent from the decision of the HREC is recorded in the minutes.

13.6. To encourage free and open discussion and to emphasise the collegiate character of the HREC, particular views are not attributed to particular individuals in the minutes, except in circumstances where a member seeks to have their opinions or objections recorded.

13.7. An HREC member unable to attend a meeting may submit comments in writing on agenda items to the Executive Officer or Chairperson prior to the meeting. Submission of written comments is recorded in the minutes.

HREC 014: Decisions available to the HREC

14.1. The HREC selects one of the following decisions on any application reviewed at a meeting and the decision is recorded in the minutes:

a) Approve the application as being ethically and scientifically acceptable;

b) Request modification or further information/clarification;

c) Seek further advice from external expert reviewer(s); or

d) Reject the application.

14.2. The Chairperson ensures that one of the above decisions is made on every application considered at an HREC meeting.

14.3. Where the HREC decides that further information or clarification is required, the Chairperson ensures that:

a) Further information or clarification required is specifically identified at the meeting; and

b) Delegation of responsibility for considering the further information or clarification and confirming the final HREC opinion is clearly agreed, i.e. the information will need to be re-submitted to the full HREC, a number of HREC members or the HREC Executive Committee.

HREC 015: Minutes

15.1. The Executive Officer prepares the minutes of the HREC meeting in consultation with the Chairperson and other members as necessary. The minutes are subsequently approved by the Chairperson within 10 working days of the meeting.

15.2. The minutes reflect each item listed for discussion on the agenda:

a) Attendance and apologies;

b) Declarations of conflicts of interest relating to agenda items;

c) Confirmation of minutes of the previous HREC meeting;

d) Business arising since the previous meeting(s) that the HREC indicated it wished to reconsider;

e) Minutes of meetings and any issues for noting and/or approving from the HREC Executive Committee, subcommittees and external expert reviewers;

f) Amendments to documents or modifications to applications and research projects;

g) Annual progress reports and final reports; and

h) Reports of serious adverse events and suspected unexpected serious adverse reactions.

i) HREC deliberations and decisions on new applications, whether in the main text of the minutes or in attachments:

- Submission of written comments by members;
- Summaries of the advice given by expert or lead reviewers;
- Summaries of the main issues considered;
- Decisions of the HREC on the application; and
- Formal dissent from the decision of the HREC by a member and the reason for it and/or any significant minority views (i.e. 2 or more members)

j) General business; and

k) Notification of the date, time and venue of the next scheduled meeting.

15.3. The minutes are submitted at the next meeting of the HREC for ratification as a true record. Members are given the opportunity to seek amendments to the minutes prior to their finalisation.

15.4. The minutes are confidential to the HREC and are not disclosed to investigators or sponsors.

15.5. The minutes of HREC meetings are made available to the Chief Executive or their delegate and, upon request, to the Research Governance Officer of the site where the research is to be conducted.

HREC 016: Duration of HREC approval

16.1. HREC approval applies for a maximum of five years, except where action is taken to suspend or terminate the decision.

16.2. The request to extend the duration of the research project is submitted by the Co-ordinating Investigator as an amendment for review by the HREC in the first instance.

16.3. HREC approval for an extension applies for a maximum of five years, except where action is taken to suspend or terminate the decision.

HREC 017: HREC reporting requirements

17.1. The ratified minutes of each HREC meeting are forwarded to the Chief Executive or delegate.

17.2. The HREC provides an annual report to the Chief Executive or delegate, which includes:

a) Membership/membership changes;

b) Number of meetings;

c) Number of research projects reviewed, approved and rejected;

d) Monitoring procedures for ethical aspects of research in progress and issues identified by the HREC in undertaking its monitoring role;

e) Description of any appeals and complaints received and their outcome;

f) Description of any research where HREC approval has been suspended or withdrawn and the reasons for this action;

g) General issues including advice on strategies to promote awareness of the ethical conduct of human research in the institution; and

h) Resources to assist the HREC in fulfilling its role.

17.3. The HREC completes and submits reports on behalf of the Public Health Organisation to the:

a) Australian Health Ethics Committee (AHEC) in accordance with the requirements of the NHMRC; and

b) NSW Privacy Commissioner in accordance with the requirements of the *Health Records and Information Privacy Act 2002 (NSW).*

HREC 018: Clinical Trial Notification and Clinical Trial Exemption schemes

18.1. Unapproved therapeutic goods have undergone limited or no evaluation of quality, safety or efficacy by the Therapeutic Goods Administration (TGA). Use of these products is considered to be experimental and potentially carries risks that have not been defined in the Australian context.

18.2. Clinical Trials conducted in Australia are subject to various regulatory controls to ensure the safety of participants, The TGA regulate the use of therapeutic goods supplied in clinical trials in Australia under the therapeutic goods legislation https://www.tga.gov.au/legislation-legislative-instruments

18.3. Clinical Trials sponsors must be aware of the requirements to import, export and manufacture and supply therapeutic goods in Australia.

18.4. The following avenues provide for the importation into and / or supply in Australia of unapproved therapeutic goods for use in a clinical trial:

- Clinical Trial Notification (CTN) scheme and,
- Clinical Trial Exemption (CTX) scheme.

18.5. Clinical Trials that do not involve unapproved therapeutic goods are not subject to requirements of the CTN or CTX schemes. It is the responsibility of the Australian clinical trial sponsor to determine whether a product is considered an unapproved therapeutic good.

CTN/CTX HREC application requirements

18.6. The CTN scheme is a **notification** process involving the following:

- The clinical trial sponsor must notify the TGA of the intent to sponsor a clinical trial involving the use of an unapproved therapeutic good. The notification must be submitted online and accompanied by the relevant fee.
- The TGA may write to the sponsor to provide specified information related to the goods notified in the CTN form.
- The HREC reviews the scientific validity of the trial design, the balance of risk versus harm of the therapeutic good, the ethical acceptability of the trial process and approves the trial protocol. The HREC is also responsible for monitoring the conduct of the trial.
- The institution or organisation at which the trail will be conducted, referred to as the 'Approving Authority', gives the final approval for the conduct of the trial at the site, having due regard to advice from the HREC.
- It is the responsibility of the sponsor to ensure that all the relevant approvals are in place before supplying the unapproved therapeutic goods in the clinical trial.

18.7. CTN Form:

- The Online CTN Form can be accessed via the TGA business services website

- Further information about CTN can be accessed via the TGA website.

18.8. CTX Scheme is an **approval** process involving the following:

- A sponsor submits an application to the TGA seeking approval to supply unapproved therapeutic goods in a clinical trial. The application must be accompanied by the relevant fee.
- The TGA evaluates the summary information about the product including relevant, but limited, scientific data (which may be preclinical and early clinical data) prior to the start of a trial.
- The HREC is responsible for considering the scientific and ethical issues of the proposed trial protocol.
- The sponsor must notify the TGA of each trail conducted using the unapproved therapeutic goods approved in the CTX application.

18.9. CTX Form: These applications are submitted via a paper based form. There are two forms that must be completed and submitted by the sponsor and posted to the TGA. The forms can be found at CTN Forms.

18.10. Further resources on how to complete CTN and CTX can be found at Clinical guidance section on the TGA website.

18.11. The Australian Clinical Trial Handbook also provides guidance on conducting clinical trials in Australia using ‘unapproved’ therapeutic goods.

HREC 019: Authorised prescriber applications

19.1. In accordance with the *Therapeutic Goods Act 1989*, *Therapeutic Goods Regulations 1990 and Therapeutic Goods (Medical Devices) Regulations 2002,* the Therapeutic Goods Administration (TGA) is able to grant to a medical practitioner authority to prescribe a specified unapproved therapeutic good or class of unapproved therapeutic goods to specified recipients or classes of recipients (identified by their medical condition). An Authorised Prescriber can then prescribe that product for that condition (also known as the 'indication') and no approval from the TGA is required for each individual patient. For further information please refer to Authorised Prescriber Scheme – Guidance for Medical Practitioners, Human Research Ethics Committees, Specialist Colleges and Sponsors. Full details of Authorised Prescribers are available from the TGA at https://www.tga.gov.au/form/authorised-prescribers OR frequently asked questions about Authorised Prescribers https://www.tga.gov.au/frequently-asked-questions-about-authorised-prescribers

19.2. On 1st July, 2017, the TGA implemented a change to the application process of the Authorised Prescriber Scheme to streamline access to unapproved therapeutic goods. **This change removed the requirement for a medical practitioner to resubmit their clinical justification to the TGA as this is required to be submitted to and be evaluated by a Human Research Ethics Committee (HREC) or specialist college.**
The duration of approval may now also be extended for therapeutic goods which are deemed to have an established history of use – from one year to two years for medical devices and from two years to five years for medicines and biologicals, at the discretion of the Delegate who makes the decision. Please refer to the TGA website for the list of goods that are deemed to have an established history of use https://www.tga.gov.au/authorised-prescriber-scheme

19.3. Medical practitioners can become Authorised Prescribers under the Therapeutic Goods Act 1989 http://www.austlii.edu.au/au/legis/cth/consol_act/tga1989191/ and its associated regulations. Other health practitioners, including dentists, are not eligible to become Authorised Prescribers. These practitioners may be able to access unapproved therapeutic goods for individual patients under the Special Access Scheme https://www.tga.gov.au/form/special-access-scheme

19.4. To become an Authorised Prescriber, a medical practitioner must provide the following information which will need to be approved by a Human Research Ethics Committee:

1. **A completed Authorised Prescriber Scheme application Form** https://www.tga.gov.au/sites/default/files/authorised-prescriber-scheme-application-form.pdf
2. **A letter to the NBMLHD HREC Chair including the following items;**
    a. **A clinical justification** for the use of the unapproved goods for evaluation by the HREC including the indication for use, the seriousness of the condition and the expected benefits of the proposed treatment vs its risk. It should also address the circumstance where there are approved treatments for the same indication specifically:

i. Have they been attempted
ii. Will they be attempted prior to supplying the unapproved good
iii. Why are they inappropriate
iv. Why is the proposed unapproved good more appropriate than any approved available alternative
v. How the risk associated with the use of an unapproved good will be managed
    1. The monitoring that will be undertaken
    2. The process of investigation and reporting adverse events
vi. The following are **NOT** acceptable justifications for the use of an unapproved good;
    1. **That the unapproved good is less expensive**
    2. **Personal preference for an unapproved good**

b. A determination as to whether any suitable alternative marketed goods are available on the ARTG
c. **Details of the medical practitioner** including name, contact details, qualifications (speciality training and experience), description of how they propose to use the goods. This should include details that the medical practitioner has the necessary experience to appropriately manage the medical condition and use the product. Details also on access to facilities needed to appropriately administer and monitor treatment. Please include a Curriculum Vitae (CV) with your application for the HREC review.
d. **Details of the site**(s) at which the goods will be used.
e. **Details of the unapproved good** whether it is a medicine, biologic or device including name, active ingredient, strength / concentration and dosage form (if applicable), sponsor and whether the good is approved for the indication in another jurisdiction.
f. **Details on efficacy and expected benefits,** any known / expected adverse effects, risks and safety issues and related toxicology for the unapproved good
g. **Evidence to support the use of the unapproved good** for example, product information documents (if the good is approved by an overseas regulator), randomised controlled trials, non-randomised controlled trials, individual case studies or consensus opinion of specialist colleges and societies.
h. **Informed Consent** since the use of unapproved goods is considered experimental, the Authorised Prescriber must obtain the informed consent of each patient for whom they prescribe the unapproved good. The Authorised Prescriber must advise patients':
    i. That the TGA has not have evaluated the unapproved good's safety, quality and efficacy
    ii. Of the possible benefits and risks of its use
    iii. Of the possibility that there may be unknown side effects
    iv. Of any alternative approved goods

Note: An informed consent template is provided if required here

Further information can be found at https://www.tga.gov.au/book-page/information-medical-practitioners#hrec

19.5. The following things need to be submitted to the HREC to obtain approval:

- Submit the completed Authorised Prescriber Application Form, **PLUS**

Letter to the NBMLHD HREC Chair, outlining all the above listed items in section 2 (a – i) above

- Email your application to the Research Office using the following email.
  NBMLHD-Ethics@health.nsw.gov.au

- Your application will be considered at the next scheduled HREC meeting and you will be notified by email of the outcome. If your application is approved then you will receive a HREC approval letter. If your application is not approved or requires further information, then your letter will outline what is required.
- If you have further question you can contact;

  The NBMLHD HREC Executive Office via email or phone
  Phone: 4734 1998
  Email: NBMLHD-Ethics@health.nsw.gov.au

19.6. Once the HREC has granted approval or endorsement by a specialist college, an application can be made to the TGA to become an Authorised Prescriber. The application must include:

- The HREC letter of approval or specialist college endorsement that must include a declaration that all necessary documentation has been reviewed by the HREC
- A completed application form
- Submit to the TGA via post or email;
  - Email
    EPS@health.gov.au

  - Post to

    Medicines Shortage Section
    Pharmacovigilence and Special Access Branch
    Therapeutic Goods Administration
    PO BOX 100
    Woden ACT 2606
    Australia

19.7. The TGA either authorises or does not authorise applications. Either way the decision will be advised via a letter stating the information relevant to prescribing the unapproved good.

19.8. Together with the TGA authorisation, a periodic reporting template will be issued so that as an Authorised Prescriber of an unapproved good, there is a requirement to submit 6 monthly supply reports and report any adverse reactions to the TGA.

19.9. Unapproved therapeutic goods generally have not been evaluated for safety, quality and efficacy and could pose unknown risks. As an Authorised Prescriber any adverse event or product defect related to the unapproved good must be reported to the TGA within 15 calendar days of learning of it. These events should also be reported to the NBMLHD HREC.

19.10. For the reporting of adverse events to the TGA please see the following link for further information specific to the reporting requirements https://www.tga.gov.au/reporting-adverse-events

19.11. Once you have been authorised by the TGA as an Authorised Prescriber you may start prescribing that good to patients under your care.

19.12. The HREC will review its endorsement of the Authorised Prescriber if it is aware of:

a) Inappropriate use of the product by the Authorised Prescriber;
b) Safety concerns about the product;
c) Failure of the Authorised Prescriber to comply with conditions imposed by the HREC; or
d) Failure of the Authorised Prescriber to comply with legislation.

19.13. Where the HREC is satisfied that the welfare and/or rights of patients are not or will not be protected, it will:

a) Advise the medical practitioner and the Chief Executive of its concerns;
b) Withdraw its approval of the Authorised Prescriber if it is satisfied that the welfare and/or rights of patients are not or will not be protected; and
c) Report to the TGA (Chief Executive and Chairperson to determine).

19.14. To review access to unapproved therapeutic goods via Authorised Prescribers, the HREC and Public Health Organisation will determine the best process for considering applications. This process may consist of:

a) Determination by the HREC Executive Committee; and/or
b) Consultation with the hospital drug and therapeutics committee or delegate; and/or
c) Consultation with the scientific subcommittee.

19.15. Decisions by the HREC Executive Committee are tabled for ratification at the next HREC meeting.

Institutional approval

19.16. Final responsibility for the use of an unapproved product within an institution always rests with that institution. Medical practitioners working in a NSW Public Health Organisation should discuss the use of the unapproved therapeutic product and identify the approval process with the institution before applying for authorisation.

HREC 020: Special Access Schemes

20.1. The Special Access Scheme (SAS) refers to the arrangements which provide for the import and/or supply of an unapproved therapeutic good on a single patient, case-by-case basis under of the *Therapeutic Goods Act 1989*, *Therapeutic Goods Regulations 1990 and Therapeutic Goods (Medical Devices) Regulations 2002*. Full details of SAS are available from the Therapeutic Goods Administration (TGA) at http://www.tga.gov.au/hp/sas.htm.

20.2. For the purposes of SAS, patients are categorised as follows:

a) Category A patients: "persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment". Medical practitioners can import and/or supply the unapproved therapeutic goods to this category of patient, having obtained the informed consent of the patient or the patient's legal representative, without the approval of the TGA but the TGA must be notified using the Category A Form Special Access Scheme form.

b) Category B: "all other patients". Medical practitioners must obtain approval from a delegated medical officer within the TGA or a delegate outside the TGA (external delegate) to import and/or supply the unapproved therapeutic good.

20.3. The choice of categorisation lies with the prescriber.

'External Delegates'

20.4. When seeking approval to supply unapproved therapeutic goods to a single patient, if appropriate, medical practitioners may apply to a nominated 'external delegate' An 'external delegate' is a person external to the TGA, given the delegation to approve the supply of unapproved therapeutic goods.

20.5. HREC responsibilities in relation to SAS are primarily concerned with granting approvals under section 19(1)(a) of the *Therapeutic Goods Act 1989*. In accordance with *Therapeutic Goods Regulation 1990* 47A (6)(b) and *Therapeutic Goods (Medical Devices) Regulations 2002* 10.6(6)(b), all SAS applications approved by an 'external delegate' must be approved by an HREC. In practice, external delegations are rare and thus HRECs are not asked to deliberate on such issues as a routine matter.

20.6. Before agreeing to an approval by an 'external delegate', the HREC should be provided with the following information:

a) The product for which approval is sought;

b) Whether that unapproved product is included on the list of products which can be approved by the practitioner;

c) Details about the product to be prescribed, including an assessment of the efficacy and safety of the product;

d) The medical condition for which approval is sought;

e) An assessment of the seriousness of the condition treated;

f) The intended mode of use/treatment and whether this conforms to the treatment protocol; and

g) The clinical justification for use of the unapproved product, including the nature and availability of alternative treatments.

20.7. Further details on the role of HREC in agreeing to an approval by an 'external delegate' are provided in the TGA *Human Research Ethics Committees and the Therapeutic Goods Legislation,* June 2001.

20.8. The HREC and Public Health Organisation will determine the best process for considering request for approval by an external delegate. This process may consist of:

a) Determination by the HREC Executive Committee; and/or

b) Consultation with the hospital drug and therapeutics committee; and/or

c) Consultation with the scientific subcommittee.

20.9. Decisions by the HREC Executive Committee are tabled for ratification at the next HREC meeting.

Institutional approval

20.10. Final responsibility for the use of an unapproved product within an institution always rests with that institution. Medical practitioners working in a NSW Public Health Organisation should discuss the use of the product and the approval process with the institution before applying for authorisation.

HREC 021: Biomedical engineering assessment of equipment / devices

Purpose: To describe the procedure to obtain clearance from a Biomedical Engineer for the use of non-TGA approved electromedical equipment / devices in clinical trials.

These guidelines apply to all studies using devices, including clinical trials being undertaken for clinical trial groups, independent research institutes, collaborative groups or investigator-initiated trials.

The types of devices that require a biomedical engineering review are any non-TGA approved equipment/devices (and accessories) that make physical or electrical contact with the patient or transfer energy to or from the patient, or detect such energy transfer to or from the patient, or are intended to diagnose, treat or monitor a patient.

Specific exclusions are surgical instruments such as retractors, clamps, forceps, needles, scalpels etc.

21.1 When submitting applications to the NBMLHD HREC a copy of their research application will be submitted by the HREC Executive Officer to a Biomedical Engineer at NBMLHD requesting confirmation of compliance with required standards, along with the following:

- A copy of the HREC application and study protocol
- The device - for review and return to the researchers
- Manuals, specifications and known standards of the device

21.2 The HREC Executive Officer will submit any specific information on the equipment / device provided by the investigator and requested by the Biomedical Engineer.

21.3 The Biomedical Engineer will peruse the material provided and confirm that the equipment / device complies with the required standards. The HREC Executive Officer will receive this information.

21.4 Biomedical review and approval should be received prior to the study proceeding for ethical review to the HREC or in parallel as the submission proceeds through the ethical review process.

HREC 022: Notification of HREC decisions

22.1. The procedures outlined in this section apply to notification of the outcome of full and expedited HREC review.

22.2. Following confirmation of the minutes by the Chairperson, the Co-ordinating Investigator will be notified of the decision in writing within 10 working days of the meeting.

Requests for modification/further information

22.3. The following information will be included in the letter of notification:

a) The decision reached by the HREC or HREC Executive Committee;

b) Requests for modification of or further information for the research project with reference to the *National Statement* or relevant legislation where necessary and the process for approval of the modifications as agreed by the HREC or HREC Executive Committee; and

c) Notification that a response be provided within 3 months or two HREC meetings (whichever occurs sooner). After this time the application is considered withdrawn and the Co-ordinating Investigator will be required to submit a new application.

Approved research projects

22.4. Final approval for a research project will be given at:

a) the full HREC meeting where the application was initially considered; or

b) the full HREC meeting where the response to a request for modification/ further information was considered; or

c) the HREC Executive Committee meeting where the low and negligible risk application was initially considered; or

d) the HREC Executive Committee meeting where the response to a request for modification/further information was considered.

22.5. The following information will be included in the approval letter:

a) The decision reached by the HREC or HREC Executive Committee;

b) A list of all approved documents including version numbers and dates;

c) A list of all sites for which the ethical and scientific approval applies;

d) Duration of ethical and scientific approval;

e) Confirmation that the HREC composition is in accordance with the *National Statement*; and

f) A statement to the effect that the project cannot commence at a NSW public Health site until site authorisation is granted.

22.6. Additional approval conditions specified by the HREC or HREC Executive Committee for a particular application, for example a requirement for more frequent progress reports, will be included in the approval letter.

22.7. The opinion of the HREC or the HREC Executive Committee forms part of the recommendation to the Chief Executive or delegate to authorise the conduct of research at a NSW Public Health Organisation. The research will not commence until this authorisation has been granted.

22.8. Approved projects will be expected to commence within 12 months of the date on which a favourable ethical and scientific decision is given by an HREC. A project commences when any study procedure or any part of the protocol is implemented at a site.

22.9. Where the project does not commence within 12 months, the Co-ordinating Investigator will provide the HREC with an explanation in the annual progress report.

Rejected research projects:

22.10. Where the research project is rejected, the following information will be included in the letter of notification:

a) The decision of the HREC or HREC Executive Committee;

b) Full explanation of reasons by reference to the *National Statement* or relevant legislation where necessary; and

c) Advice regarding available options for further review.

HREC 023: Adverse event reporting

Clinical trials involving therapeutic products

23.1. In November 2016, the National Health and Medical Research Council (NHMRC) overhauled their safety reporting advice, and produced the document Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods, which replaced the Australian Health Ethics Committee's 2009 Position Statement, Monitoring and reporting of safety for clinical trials involving therapeutic products.

The new Guidance has been endorsed by the Therapeutic Goods Administration.

This updated NHMRC Guidance restructures safety reporting responsibilities of key stakeholders and amends reporting pathways that previously placed an unnecessary burden on Australian investigators and Human Research Ethics Committees (HRECs) while not genuinely contributing to patient safety.

In response, NSW Health has issued a new Policy Directive (PD2017_039) titled Safety Monitoring and Reporting for Clinical Trials Conducted in NSW Health Organisations (released on 27/10/2017). The new Policy can be found here http://www1.health.nsw.gov.au/pds/ActivePDSDocuments/PD2017_039.pdf

23.2. NSW Public Health organisations implemented the new safety monitoring and reporting policy for all active trials as of 3rd of October 2017.

For more information regarding safety monitoring and reporting guidelines, please refer A letter from Dr Tony Penna, Executive Director of Office for Health and Medical Research, informing sponsors.

23.3 **What changes to reporting requirements have been made?**

- Fewer reports will be required
- All safety reporting to the HREC and / or RGO is the responsibility of the sponsor or their delegate (e.g. The Principal Investigator).

Key Changes:

- **HRECs will no longer receive**: Single case Adverse Events (AEs), Serious Adverse Events (SAEs) /Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reaction (SUSARs)*, or device/non-therapeutic good trial equivalents or six monthly line listings.
- **HRECs will receive**: All significant safety issues (SSIs), annual safety reports and investigator's brochure updates. These will be submitted to the HREC by the sponsor or their delegate [e.g. The Coordinating Principal Investigator (CPI) or Principal Investigator PI)].

  Forms to use

  - NBMLHD SSI notification Form
  - NBMLHD Annual Progress Report or Sponsors template

- **Research Governance Office's will no longer receive:** Single case AEs, SAE/SARs, and external SUSARs* or device/non-therapeutic good equivalents or six monthly line listings.
- **Research Governance Office's will receive**: all significant safety issues (SSIs), any local SUSARs/USADSs/URSAEs and any research related events that meets the definition of an incident (PD2014_004).

*Note – If an SAE/SAR/SUSAR meets the definition of an SSI, it will be reported to the HREC/RGO through that reporting mechanism.

Forms to use

- NBMLHD SSI notification Form
- NBMLHD SUSAR/USADE/URSAE Notification Form

23.4. **Key Definitions:**

- **Therapeutic Goods Trials:** Trials investigating the safety and/or effectiveness of medicines, biologicals or medical devices.
- **Non-Therapeutic Goods Trials:** Trials other than a Therapeutic Goods Trial (e.g. radiotherpay, surgery, psychotherapy trials).
- **Suspected Unexpected Serious Adverse Reaction (SUSAR):** An adverse reaction that is both serious and unexpected.
- **Unanticipated Serious Adverse Device Effects (USADEs):** A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (and/or Investigator's Brochure/Instructions for Use).
- **Urgent Safety Measure (USM):** A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.
- **Significant Safety Issue (SSI):** A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
- **Unexpected & Related SAEs (URSAE):** An adverse event that is:
  - **Serious –** meets the definition of a serious adverse event
  - **Related –** resulted from administration of the trial intervention
  - **Unexpected –** the event is not described in the protocol as an expected occurrence.

Frequently asked Questions:

The safety monitoring and reporting FAQs provide information to facilitate the consistent implementation of the OHMR guidance in NSW. Please see http://www.health.nsw.gov.au/ethics/Pages/safety-faq.aspx for further detailed information.

Safety reporting Pathway for all trials:
http://www.health.nsw.gov.au/ethics/Pages/safety-pathways.aspx

23.5. Depending on the complexity, design and risk perceived, the reviewing HREC and/or the Public Health Organisation has the discretion to require that additional information be reported.

Figure 1: Reporting Pathway for Therapeutic Goods trials

As illustrated below, sponsors may report directly to NSW HRECs; however, they must ensure that all communications sent to the HREC adequately identify the trial and provide context in relation to the HREC's role (e.g. whether there is any impact on patient safety, trial conduct or trial documentation)

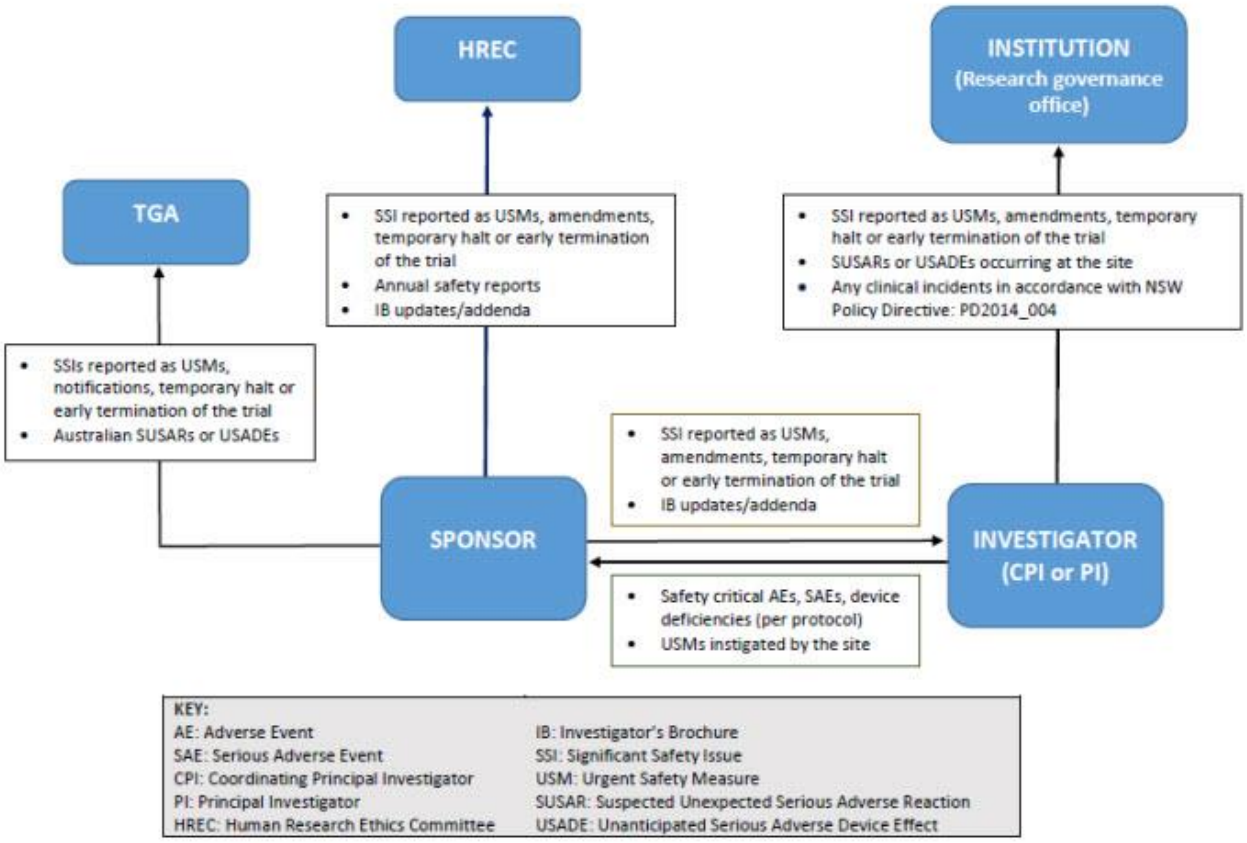

Table 1 – Summary of safety notifications to the HREC and RGO (therapeutic goods trails)

Type of Event	Who Reports	To Whom	When	How
Significant Safety Issue (SSI) Implemented as an Urgent Safety Measure (USM)	Sponsor / Delegate	The reviewing HREC (and all Investigators participating in the study)	As soon as possible and no later than 72 hours of the sponsor becoming aware of the USM	NBMLHD SSI Notification Form or sponsor template
Significant Safety Issue (SSI) not implemented as an Urgent Safety Measure (USM)	Sponsor / delegate	The reviewing HREC (and all Investigators participating in the study)	Within 15 days of the sponsor becoming aware of the SSI	NBMLHD SSI Notification Form or sponsor template
All Significant Safety Issues (SSIs)	Principal Investigator	The RGO for the site where the event occurred	As soon as possible and no later than 72 hours of the PI becoming aware of the SSI	NBMLHD SSI Notification Form or sponsor template
Suspected Unexpected Serious Adverse Events (SUSARs) and Unanticipated Serious Adverse Device Effects (USAEDEs) occurring at the site	Principal Investigator	The RGO for the site where the event occurred	Within 72 hours of the PI becoming aware of the event	NBMLHD SUSAR/USADE/URSAE Notification Form
Investigator Brochure Updates /Addenda	Sponsor / Delegate	The reviewing HREC	As and when updated are generated	Submitted with a cover sheet or as part of an annual progress / annual safety report
Annual Safety Report	Coordinating Principapl Investigator	The reviewing HREC	Within annual progress report sent to the HREC or aligned with the safety reporting cycles of global companies	NBMLHD Annual Progress Report or sponsors template

Text Alternative for above Information Figure 1 and Table 1:

Reporting pathway for therapeutic goods trials

The safety reporting flowchart (Figure 1) for therapeutic trials illustrates the safety reporting responsibilities of the Sponsor and the Investigator to the Institution, HREC and TGA.

The Investigators responsibilities are to report:

- all safety critical Adverse Events (AE), Significant Adverse Events (SAE), device deficiencies per protocol and Urgent Safety Measures (USM) instigated by the site to the Sponsor and
- all Significant Safety Issues (SSI), Urgent Safety Measures (USM), amendments, temporary halt or early termination of the trial, Suspected Unexpected Serious Adverse Reactions (SUSAR) Unanticipated Serious Adverse Device Effect (USADE) occurring at the site and any clinical incidents in accordance with NSW Policy Directive (PD2014_004) to the Institution (Research Governance Office).

The Sponsor's responsibilities are to report:

- all Significant Safety Issues (SSI), Urgent Safety Measures (USM), amendments, temporary halt or early termination of the trial and Investigator's Brochure (IB) updates to the Investigator
- all Significant Safety Issues (SSI), Urgent Safety Measures (USM), amendments, temporary halt or early termination of the trial, annual safety reports and Investigator's Brochure (IB) updates to the HREC and
- all Significant Safety Issues (SSI), Urgent Safety Measures (USM), amendments, temporary halt or early termination of the trial and Suspected Unexpected Serious Adverse Reactions (SUSAR) Unanticipated Serious Adverse Device Effect (USADE) occurred in Australia to TGA.

Figure 2 – Reporting Pathway for non-therapeutic goods trials

As illustrated below, sponsors may report directly to NSW HRECs; however, they must ensure that all communications sent to the HREC adequately identify the trial and provide context in relation to the HREC's role (e.g. whether there is any impact on patient safety, trial conduct or trial documentation).

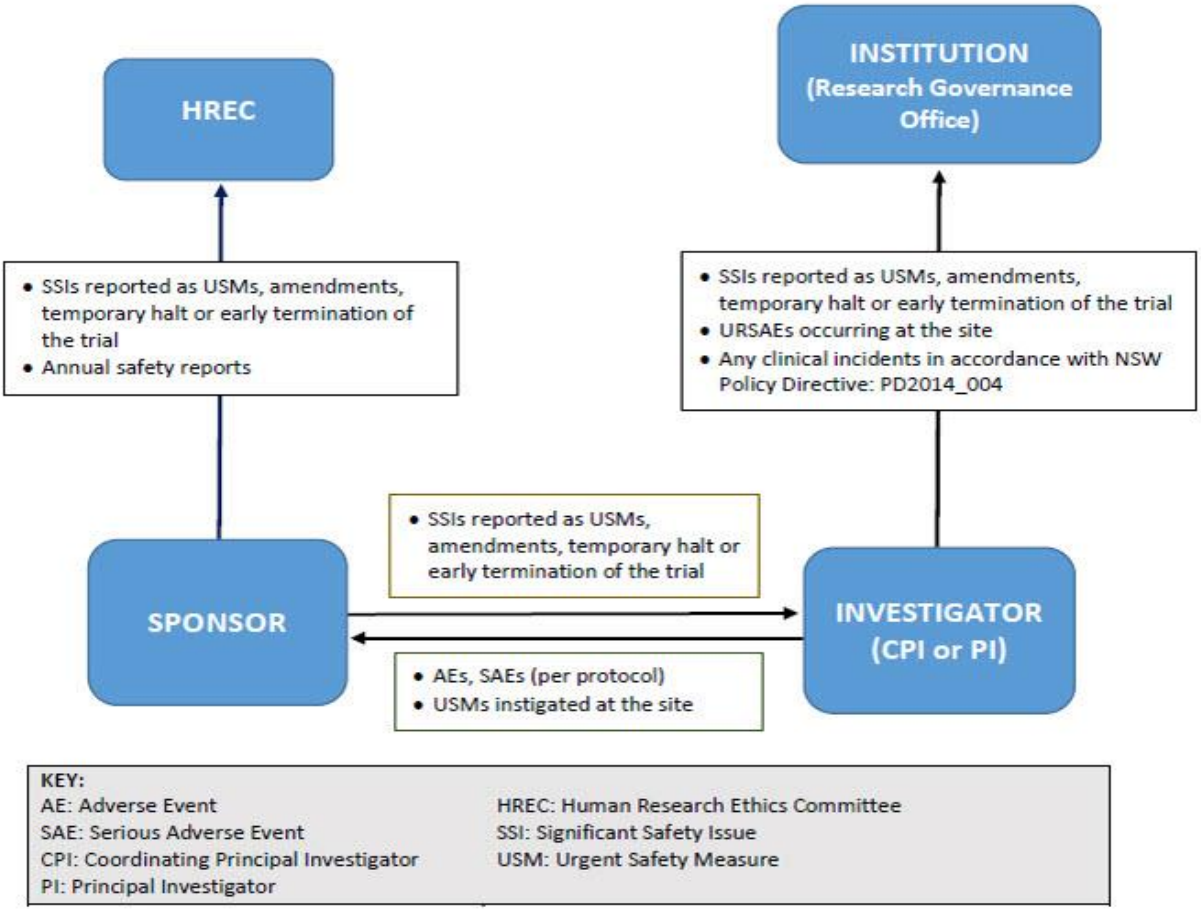

Table 3 – Summary of safety notifications to the HREC and RGO (non-therapeutic goods trails)

Type of Event	Who Reports	To Whom	When	How
Significant Safety Issue (SSI) Implemented as an Urgent Safety Measure (USM)	Sponsor / Delegate	The reviewing HREC (and all Investigators participating in the study)	As soon as possible and no later than 72 hours of the sponsor becoming aware of the USM	NBMLHD SSI Notification Form or sponsor template
Significant Safety Issue (SSI) not implemented as an Urgent Safety Measure (USM)	Sponsor / delegate	The reviewing HREC (and all Investigators participating in the study)	Within 15 days of the sponsor becoming aware of the SSI	NBMLHD SSI Notification Form or sponsor template
All Significant Safety Issues (SSIs)	Principal Investigator	The RGO for the site where the event occurred	As soon as possible and no later than 72 hours of the PI becoming aware of the SSI	NBMLHD SSI Notification Form or sponsor template
Unexpected & Related Serious Adverse Event (URSAEs) occurring at the site	Principal Investigator	The RGO for the site where the event occurred	Within 72 hours of the PI becoming aware of the event	NBMLHD SUSAR/USADE/URSAE Notification Form
Annual Safety Report	Coordinating Principal Investigator or Sponsor Delegate	The reviewing HREC	Annually (within the Annual Progress Report)	NBMLHD Annual Progress Report

Text Alternative to above Information Figure 2 and Table 2

Reporting pathway for non-therapeutic goods trials

The safety reporting flowchart for non-therapeutic trials illustrates the safety reporting responsibilities of the Sponsor and the Investigator to the Institution and HREC.

The Investigators responsibilities are to report:

- all safety critical Adverse Events (AE), Significant Adverse Events (SAE) and Urgent Safety Measures (USM) instigated by the site to the Sponsor and
- all Significant Safety Issues (SSI), Urgent Safety Measures (USM), amendments, temporary halt or early termination of the trial, Unexpected & Related SAEs (URSAE) occurring at the site and any clinical incidents in accordance with NSW Policy Directive (PD2014_004) to the Institution (Research Governance Office).

The Sponsor's responsibilities are to report:

All Significant Safety Issues (SSI), Urgent Safety Measures (USM), amendments, temporary halt or early termination of the trial and annual safety reports to the HREC.

Review of safety reports by the HREC

23.8. Safety reports will be reviewed by an HREC subcommittee (such as a scientific review committee) or HREC Executive Committee to determine the appropriate course of action.

23.9. If the HREC subcommittee or HREC Executive Committee deems further information is required it will request this from:

a) an independent expert with expertise in the area; or

b) the Co-ordinating Investigator or Principal Investigator who submitted the report with a copy to the other.

23.10. For reported deaths the HREC will, at its discretion, request information such as autopsy reports and terminal medical records.

23.11. Following review, the HREC will take the appropriate course of action which will include, but not be limited to one or more of the following:

a) Including a notation on file of the safety-related occurrence;
b) Increasing monitoring of the research project;
c) Requesting an amendment to the project and/or Participant Information Sheet and Consent Form and any other study documents;
c) Suspending ethical approval; and
d) Withdrawing ethical approval.

Notification of HREC review outcome

23.12. The HREC will inform the Co-ordinating Investigator of the outcome of the review within 10 working days of the meeting, unless immediate notification is required for urgent safety reasons.

23.13. For multi-centre research projects, the Co-ordinating Investigator will provide a copy of the HREC review outcome to the Principal Investigators involved in the study. Each Principal Investigator will provide a copy of this HREC review outcome to the site Research Governance Officer.

23.14. The HREC has the discretion to notify the review outcome directly to the Principal Investigators and Research Governance Officers for safety reasons, in which case the Co-ordinating Investigator will be informed of this action.

HREC: 024 Monitoring approved research projects

24.1. The HREC will monitor approved research projects to ensure compliance with the conditions of approval and to protect the rights, safety and welfare of participants. This includes review of annual progress reports and final reports, safety reports and reports of protocol violations.

24.2. The HREC has the discretion to adopt other appropriate mechanisms for monitoring depending on the complexity, design and risk perceived, including:

a) Discussion of relevant aspects of the project with the investigators, at any time;

b) Random inspections of research sites, data, or consent documentation;

c) Interviews with research participants or other forms of feedback from them; and

d) Request and review reports from independent agencies such as a Data and Safety Monitoring Board.

24.3. The HREC will, at its discretion, recommend in the letter of approval that the site co-ordinates on-site monitoring at recommended intervals or randomly throughout the project.

Annual progress reports

24.4. Annual progress reports will be submitted to the reviewing HREC by the Coordinating Investigator. The first report will be submitted 12 months from the date of ethical approval.

24.5. For a multi-centre research project Principal Investigators, at sites for which the HREC has given ethical and scientific approval, will submit annual progress reports to the Co-ordinating Investigator using the reporting template stipulated by the HREC. A copy of the report will be provided to the site Research Governance Officer by the Principal Investigator.

24.6. The Co-ordinating Investigator will collate site annual progress reports for submission to the reviewing HREC with comments. The Co-ordinating Investigator will notify the relevant site Research Governance Officer if a Principal Investigator does not provide the required report for inclusion into the collated annual progress report.

24.7. The Executive Officer will send a reminder letter where a report is not received by the due date. If there is no response after 30 calendar days, a second reminder letter will be sent requesting the Co-ordinating Investigator to contact the Chairperson to discuss the report. If the report is still not received after a further period of 30 calendar days, the Chairperson will consider further action.

The NBMLHD HREC will suspend or withdraw ethical approval of a research application as information comes to hand regarding each situation.

- Where ethical approval is to be withdrawn:

(a) The HREC will request the researcher to submit a plan and revised documents for informing participants (if appropriate).
(b) The institution will see that the investigator promptly suspends the research and makes arrangements to meet the needs of the participants.
(c) An investigator cannot continue with the research if ethical approval has been suspended or withdrawn and must comply with any special conditions imposed by the institution or the HREC. The research may not be resumed unless either:
    - the researcher subsequently establishes that continuance will not compromise participants' welfare; or
    - the research is modified to provide sufficient protection for participants, the modification is ethically reviewed, and the modified research is approved.

- Where the HREC considers the research should be urgently suspended:

(a) The instruction to stop will be made by the CE of NBMLHD in association with the HREC Chair. This will be done both verbally and by letter on the day the decision to suspend withdrawal is made.
(b) The HREC will work with the investigator to explain the reasons for the immediate suspension and the requirements of the HREC to ensure the safety of participants.
(c) The HREC will meet on an ad hoc basis if necessary to discuss suspension and response/s from the investigator.

24.8. Annual progress reports will be added to the agenda and reviewed by the HREC

Executive Committee. The HREC will inform the Co-ordinating Investigator of the outcome of the review within 10 working days of the meeting, unless immediate notification is required.

24.9. For a multi-centre research project, the Co-ordinating Investigator will provide a copy of the HREC review outcome to the Principal Investigators involved in the project. Each Principal Investigator will provide a copy of this HREC correspondence to the site Research Governance Officer.

24.10. The HREC will have the discretion to notify the review outcome directly to the Principal Investigators and Research Governance Officers, in which case the Coordinating Investigator will be informed of this action.

24.11. The HREC will have the discretion to request more frequent progress reports,

depending on the complexity, design and risk perceived.

Final reports

24.12. Final reports will be submitted to the reviewing HREC by the Co-ordinating Investigator, using the reporting template stipulated by the HREC, upon completion of the research project. Final reports will include a copy of the final results and publications if available. If project data and interpretation are fully addressed in a publication, a separate copy of final results will not be required.

24.13. For a multi-centre research project Principal Investigators, at sites for which the HREC has given ethical and scientific approval, will submit final site reports to the Co-ordinating Investigator using the reporting template stipulated by the HREC. A copy of the report will be provided to the site Research Governance Officer by the Principal Investigator.

24.14. The Co-ordinating Investigator will collate final site reports for submission to the reviewing HREC, upon completion of the project at all sites with comments. Final reports will include a copy of the final results from all sites for which the HREC has given ethical and scientific approval, and publications if available. If project data and interpretation are fully addressed in a publication, a separate copy of final results will not be required.

24.15. Final reports will be added to the agenda and reviewed by the HREC Executive Committee. The HREC file will be archived as an electronic and/or hard copy, according to the Public Health Organisation's archiving policy, once the final report is acknowledged.

Protocol deviation/violation reports:

24.16. Protocol deviations are minor or administrative departures from HREC approved protocol procedures whereby data is unusable or not available, but which do not affect the scientific soundness of the research plan or the rights, safety, or welfare of research participants. Examples include: follow up visits that occurred outside the protocol required time frame because of the participant's schedule, or blood samples obtained at times close to but not precisely at the time points specified in the protocol.

24.17. At the discretion of the Co-ordinating Investigator (or Principal Investigator in the case of multi-centre research) a list of protocol deviations may be reported with the annual progress report, however this is not a requirement.

24.18. Protocol violations are instances where the protocol requirements and/or regulatory guidelines were not followed, and are generally more serious in nature than protocol deviations. Protocol violations are considered to potentially affect the scientific soundness of the research plan and/or the rights, safety, or welfare of research participants. Examples include: failure to obtain participant consent and participant inclusion/exclusion violations.

24.19. Principal Investigators will provide to the HREC written reports of protocol violations in a timely manner. The Principal Investigator will provide a copy of the report and any responses from the HREC to the Research Governance Officer.

HREC: 025: Payment of fees

25.1. Review of applications and amendments by the HREC will be subject to a fee.

25.2. The fees structure is outlined in PD2008_030 *HREC and Research Governance: Fee Policy for Review of Commercially Sponsored Research*

25.3. The Co-ordinating Investigator will provide the HREC with details of the sponsor organisation to which the invoice will be sent.

25.4. The HRECs will determine whether the invoices will be paid at the time of application.

25.5. The HREC will determine whether to withhold a letter of approval until the fee is received.