SUBMISSION OF HUMAN RESEARCH ETHICS APPLICATION

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- This guideline provides assistance to any person submitting a research ethics application to the Human Research Ethics Committee for scientific and ethical review and approval.
- Guidance is provided on development of a research application, submission and review, as well as post-approval processes.
- This Guideline is to be read in conjunction with the Policy, Research – Ethical and Scientific Review of Human Research

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	31 May 2016	**Review Period**: 3 years
Team Leader:	Executive Officer	**Area/Dept**: Research Ethics

CHANGE SUMMARY

- Nil

READ ACKNOWLEDGEMENT

- Read Acknowledge Only – All persons submitting a research ethics application to the Sydney Children's Hospitals Network Human Research Ethics Committee

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Purpose

This Guideline provides advice to any person, staff member or student who intends on submitting an application to the Research Ethics Office for ethical review by the HREC. This document is a guideline only and each application is considered on its individual merit.

1 Key Definitions

APREG is the Australian Paediatric Research Ethics and Governance Network

Certified HREC is an HREC that is hosted by an institution that has been certified by the *National Health and Medical Research Council* to participate in the national approach to single ethical review.

Coordinating Investigator is an individual who takes overall responsibility for the research project and submits the project for ethical and scientific review. The Coordinating Investigator is responsible for ongoing communication with the HREC and passing on any outcomes from this to the Principal Investigators. For single centre research, Coordinating Investigator and Principal Investigator are synonymous.

Electronic signatures are simply electronic confirmations of identity. This definition is broad enough to encompass all forms of electronic identification, from biometric signatures such as iris scans and fingerprints to non-biometric signatures, such as digital signatures. Electronic signatures must serve the same essential function that we expect of documents signed by handwritten signatures. In the digital realm, integrity means ensuring that a communication has not been altered in the course of transmission. It is concerned with the accuracy and completeness of the communication. The recipient of an electronic communication must be confident of a communication's integrity before they can rely on and act on the communication.

GCP is Good Clinical Practice

Human Research is research conducted with or about people, or their data or tissue as described in the *National Statement on Ethical Conduct in Human Research*.

Local HREC is a HREC established by a NSW Public Health Organisation to provide ethical and scientific review of human research to be conducted at sites under its control.

Lead HREC is a local HREC accredited by the Secretary of the NSW Ministry of Health to conduct ethical and scientific review of human research on behalf of the NSW public health system in the categories of:

i. Clinical trials / interventional clinical research; and / or

ii. General research

Multi-Centre Research is research that is conducted at more than one site within the NSW public health system, where those sites are within the jurisdiction of more than one NSW Health HREC.

Multi-Jurisdictional Research is research that is conducted at more than one public health organisation site that includes States outside NSW. Those states include Victoria, Queensland and South Australia. Throughout this document multi-jurisdictional will be referred to as multi-centre

National Mutual Acceptance (NMA) Scheme is single ethical review for multi-jurisdictional research in participating sites.

NSW Health HREC is a Human Research Ethics Committee (HREC) established by a NSW Public Health Organisation and registered with the National Health and Medical Research Council.

Principal Investigator is the individual who takes responsibility for the overall conduct, management, monitoring and reporting of research conducted at a site and submits the research project for site authorisation.

Public Health Organisation (PHO) under the Health Services Act 1997 (NSW), a local health district, statutory health corporation or affiliated health organisation in respect of its recognised establishments and recognised services.

Research Governance Officer is the individual appointed within the NSW Public Health Organisation who is responsible for the management of applications for site authorisation and oversight of authorised research projects.

Single Centre Research is research that is conducted at only one site within the NSW public health system (i.e. single site research) or at two or more sites under the jurisdiction of a single NSW Health HREC.

2 Introduction

The Sydney Children's Hospitals Network Human Research Ethics Committee (HREC) is responsible for ensuring ethical and scientific acceptability of research conducted at sites within the Sydney Children's Hospitals Network (SCHN) and for paediatric specific research referred to it by a NSW Public Health Organisation which involves the use of human participants, human tissue or personally identifiable records.

All research includes any conducted by SCHN staff within the Network, or external, including, but not limited to:

- As part of a staff member's role within SCHN or in which CHW or SCH contact details will be used;
- Research involving or about SCHN patients, their friends and / or family; and,
- Any research involving staff, volunteers or their families (this includes staff surveys and questionnaires)

It is the responsibility of the Researcher to ensure that ethical approval has been given, and that Site Specific Authorisation (SSA) has been received from the Chief Executive or their delegate before the research project can commence.

There are six (6) sites within the Sydney Children's Hospitals Network:

- The Children's Hospital at Westmead
- Sydney Children's Hospital, Randwick
- Newborn Emergency Transport Service (NETS)
- Bear Cottage
- The Children's Court Clinic
- NSW Pregnancy and Newborn Services Network

2.1 Research Ethics and Research Governance – What is the difference?

The SCHN Research Ethics Office and Research Governance Office operate as separate business units, but work closely to ensure appropriate pre- and post-approval oversight process for research conducted within the SCHN. As the units operate independently there are differences in forms policy and process which Investigators should be aware of.

At the most basic level:

Research Ethics is concerned with the merit and integrity of the research, the protection of participants (i.e. their welfare, the risks are outlined and benefits acknowledged) and researchers in the conduct of the research (i.e. appropriate risk management processes are in place to protect against risk and injury, e.g. needle stick).

Research Governance involves analysis and assessment of risk to the organization including financial, legal and insurance considerations.

The units continually review their processes and procedures together to reduce duplication of information where possible.

3 Policy, Guideline and Procedure Documents

The policies, guidelines and procedure documents which support this Guideline are:

Sydney Children's Hospitals Network Documents

- Research – Ethical and Scientific Review of Human Research
- Research – Authorisation of Proposals to Conduct Research on Humans (1/A/15:9060-01:00*)*
- Human Research Ethics Committee (HREC) – Standards for Review of Clinical Trials
- Human Research Ethics Committee (HREC) – Ethical Review for External Entities
- Fees for the Review of Ethics and Site Specific Assessment Applications
- Safety Reporting for Clinical Trials
- Human Tissue – Requirements of the Human Tissue Act
- SCHN HREC Standard Operating Procedures (under development)
- SCHN HREC Terms of Reference
- SCHN SAC Terms of Reference

NSW Ministry of Health Documents

- Ethical Review for External Entities
- Operations Manual – Human Research Ethics Committee Executive Officer
- Standard Operating Procedures – Human Research Ethics Committee (until such time that the SCHN HREC Standard Operating Procedures have been endorsed)
- Standards for Scientific Review of Clinical Trials
- Research – Ethical and Scientific Review of Human Research in NSW Public Health Organisations
- Quality Improvement & Ethical Review: A Practice Guide for NSW

- Research – Human and Animal Research and the National Health and Medical Research Council Act 1992
- Requirements of the Human Tissue Act 1983 in relation to research and use of tissue

National Guidelines

- The National Statement on Ethical Conduct in Human Research (2007) (herein known as 'the National Statement')
- The Australian Code for the Responsible Conduct of Research

4 Ethical & Scientific Review Framework

All human research that takes place in a NSW Public Health Organisation (PHO) must be reviewed, and approved, in accordance with the *National Statement on Ethical Conduct in Human Research (2007)* [the National Statement] and Policy Directive PD2010_056 *Authorisation to commence human research in NSW Public Health Organisations.*

The SCHN has established two (2) pathways for ethical and scientific review in accordance with these policies and guidelines:

- Full Review by the HREC
- Expedited review through the HREC Executive for Low / Negligible Risk research

4.1 Single Ethical & Scientific Review

In 2007, NSW Health introduced single ethical and scientific review into NSW PHOs in accordance with the *National Statement* guideline for minimising the duplication of ethical review (Chapter 5.3). This meant that any given NSW PHO Ethics Committee *should* accept the scientific and ethical review of a research ethics application undertaken by a lead HREC, even where that HREC is not its own local HREC.

There are some exclusions to the single ethical and scientific review framework; these being:

1. Any human research project involving persons in custody in NSW and / or staff of NSW Justice Health;

   All medical research involving persons in custody in NSW and / or staff of NSW Justice Health require review by the NSW Justice Health HREC.

   Research projects only involving persons in custody and / or staff of NSW Justice Health will be reviewed by the NSW Justice Health HREC alone. Projects that also involve other participants should be reviewed by the NSW Justice Health HREC and other appropriate HRECs.

2. Research that may affect the health and wellbeing of Aboriginal people and communities.

   Approval from the Aboriginal Health and Medical Research Council Ethics Committee is required where the research project involves research concerning any of the following:

   - The experience of Aboriginal people is an explicit focus of all or part of the research;
   - Data collection is explicitly directed at Aboriginal people;

- Aboriginal people, as a group, are to be examined in the results;
- The information has an impact on one or more Aboriginal communities; or
- Aboriginal health funds are a source of funding.

The AH&MRC accepts applications at any stage in their progress through another HREC. Each investigator can decide whether they will seek AH&MRC Ethics Committee approval before submitting to other HRECs, or after approval by other HRECs, or simultaneously.

3. Research requiring access to State-wide data collections

All research projects requiring access (including linkage) to State-wide data collections owned or managed by NSW Health or the Cancer Institute (NSW) must be reviewed by the NSW Population and Health Services Research HREC.

Prior to making a submission to the NSW Population and Health Services Research HREC, researchers are required to complete a 'Data Custodian Sign-Off Form', available from the Cancer Institute NSW website, and submit this with their research proposal to the relevant Data Custodian for review and sign-off.

If the project involves data linkage by the Centre for Health Record Linkage, researchers are required to obtain a letter of support from the Centre for Health Record Linkage prior to ethics review.

4.2 National Mutual Acceptance Scheme

In 2011, the NSW Ministry of Health together with the Queensland and Victorian Departments of Health signed a Memorandum of Understanding (MoU) to introduce *National Mutual Acceptance (NMA)* of ethical and scientific review for multi-centre clinical trials in public health organisations across these three States. In November 2013, this was amended to include South Australia.

On 14 December 2015, the scope of the NMA scheme expanded to include all types of human research.

Under the NMA initiative, each proposal for a multi-centre human research project conducted across the participating States will be ethically and scientifically reviewed once by a Public Health Organisation HREC that has been certified by the NHMRC.

Public Health Organisations will continue to undertake a site-specific assessment (SSA) of all research projects that are to be conducted at institutions under their control, in compliance with the relevant jurisdictional standard operating procedures.

There are a number of exemptions to the NMA. The following types of studies will continue to be excluded from NMA because of jurisdiction-specific requirements:

- Projects involving persons in custody or staff of the jurisdictional Justice Health departments.
- Projects specifically affecting the health and wellbeing of Aboriginal and Torres Strait Islander people and communities.
- Projects requiring access to State-wide data collections
- Projects involving access to coronial material

- First Time in Human (FTIH), Phase 0 and Phase 1 Clinical Trials (in SA Only)

Low / Negligible Risk Applications

Under the NMA, applications for scientific and ethical review of studies **greater than low or negligible risk** (LNR) must be submitted on a National Ethics Application Form (NEAF) via the Online Forms website.

Multi-jurisdictional LNR Projects – May be submitted under NMA using a full NEAF application to be reviewed by a full HREC, or on an existing LNR application form submitted to each jurisdiction.

Participating Organisations

The following Public Health Organisations across the NMA initiative are certified for **paediatric** research:

Name of HREC	Location
Hunter New England HREC	NSW
Northern Sydney LHD HREC	NSW
South Eastern Sydney LHD HREC	NSW
South Western Sydney LHD HREC	NSW
Children's Health Services HREC	QLD
Women's and Children's Health Network HREC	SA
Monash Health HREC	VIC
The Royal Children's Hospital HREC	VIC

The *National Ethics Application Form (NEAF)* is required to be used for application to a Certified HREC when applying for ethics approval under National Mutual Acceptance. Please also note the following additional requirement for applications including Victorian sites:

- For studies in **Victoria**, the ***Victoria Specific Module*** must be completed in addition to the NEAF.

Please Note – National Mutual Acceptance does not negate the need to obtain **Site Specific Authorisation** from each site listed on the application at which the research will occur.

It is recommended that applications for Site Specific Authorisation be submitted in parallel to the ethics submission.

Research projects occurring across the Children's Hospital at Westmead and Westmead Adults hospitals

The Research Ethics Offices' at the Children's Hospital at Westmead and the Westmead Adults hospital have an agreement that a single application can be submitted to either

hospital, despite each not being accredited to review the other's principal patient group. Applications submitted to the Children's Hospital at Westmead that include an adult participant group at Westmead Hospital will be sent by the Research Office to the Executive Officer at Westmead Hospital for their review from an adult population perspective. The reverse will occur for applications submitted to Westmead Hospital that include a paediatric population.

5 Types of Human Research Ethics Applications

Whilst many Human Research Ethics Committees both within and external to the Public Health system require that research involving children and / or young people be reviewed by the full Committee, the SCHN HREC is a specialist Committee reviewing paediatric specific research as its core business. This being the case, applications for paediatric research can be submitted through the Low / Negligible Risk process.

Whether to submit your application as an LNR or NEAF is dependent on the conditions outlined in the NSW Health Policy Directive, the *National Statement* and the Level of Risk to the Participant as a Result of Participating in the Research Project which are reiterated below.

If you are unsure of whether your application is low or high risk, applicants should contact the Executive Officer of the SCHN HREC to discuss before completing any documentation.

5.1 Low / Negligible Risk Research Applications (LNR)

An LNR can be used where there is, as the name suggests, a low or negligible risk to participants as a result of participating in the research.

The *National Statement* describes research as being low risk where the only foreseeable risk is one of discomfort, such as minor side-effects of medication, discomforts related to measuring blood pressure or anxiety induced by an interview.

Research that is negligible is where there is no foreseeable risk of harm or discomfort; that is, unless that foreseeable risk is no more than inconvenience, for example, filling in a form or participating in a survey.

Examples of low and negligible risk research may include:

1. Research involving only questionnaires and general surveys on non-controversial, non-personal issues that also include only basic demographic data and where, in all instances, respondents are not identifiable;
2. Research involving only the use and/or disclosure of information from existing data collections, where the identity of the person cannot reasonably be ascertained from the information to be disclosed to researchers;
3. Research involving human tissue where participant consent is not required because broad consent has been provided for use of the tissue in research and specific individuals cannot be identified from specimens used; e.g. where specimens have never been labelled with individual identifiers or individual identifiers have been permanently removed; and,

4. Research requiring access to individual medical records or to informed stored electronically, through the site's medical records department or other department / specialty, but where participant consent is not required because, in all instances, individuals cannot be identified from data extracted or provided.

5.2 National Ethics Application Form (NEAF) – Research with greater than low risk

In accordance with the *National Statement*, the following types of human research **must** be ethically reviewed by the full Committee and not through an expedited process.

1. Research that involves more than a low risk to participants.
2. Research that includes any of the following:
    i. Interventions and therapies, including clinical and non-clinical trials and innovations or new treatment modalities;
    ii. Active concealment or planned deception of participants;
    iii. Exposure of illegal activities.
3. Research specifically targeting Aboriginal or Torres Strait Islander peoples.
4. Research that includes any of the following, except where the project uses collections of non-identifiable data and involves only negligible risk to participants:
    i. Human genetics;
    ii. Human stem cells;
    iii. Women who are pregnant and the human foetus;
    iv. People who are highly dependent on medical care who may be unable to give consent;
    v. People with a cognitive impairment;
    vi. People with an intellectual disability or a mental illness; and,
    vii. People who may be involved in illegal activities.

5.2.1 Scientific Review of Clinical Trials

The NSW Health Policy Directive PD2007-035 states that:

"To ensure a level of scientific review that protects the interests of research participants and is practicable, sustainable and a level appropriate to the risks of the research project being reviewed, minimum standards have been developed for the scientific review of clinical trials…All clinical trials must be scientifically reviewed in accordance with these standards before being approved by a NSW Health Human Research Ethics Committee (HREC)"

Further to this, the SCHN HREC requires that all NEAF applications being reviewed by the full HREC demonstrate some evidence of peer-review prior to submission to the Human

Research Ethics Committee for ethical review. Applications that are not able to demonstrate this will be reviewed by the SCHN Scientific Advisory Committee (SAC), a sub-committee of the HREC.

Peer Review

The Executive Officer has the delegation of the HREC to determine the scientific and ethical review path of any new applications received.

An application for ethical review is considered to have been satisfactorily peer reviewed when the applicant can demonstrate that it has been subject to rigorous review through a competitive grant funding process (i.e. a Tier 1 grant), and was either successful in receiving that grant, or characterised as a 'near miss'. Evidence must be supplied to demonstrate funding outcomes.

5.3 Clinical Case Reports

A Clinical Case Report is a low risk application that is more appropriately defined as a detailed case study of a small number of patients (less than 10) with the intention to publish.

Clinical Case Reports have a separate application form available on the Intranet and Internet.

For Clinical Case Reports, consent must be sought from the parents / guardians of the child whose information will be part of the publication. This project specific consent form must be attached to your application on submission.

Clinical Case Reports do not require Site Specific Authorisation however applicants who were not the treating clinician are required to provide evidence of support from the treating clinician in the form of a letter attached to the application.

5.4 Programs of Research

A Program of Research is defined as one of the following:

1. *A single research theme using a variety of methodologies;*
2. *A single methodological approach used to address a series of related research questions by either the same research group or a team of researchers from various disciplines;*
3. *A research bio-bank from which future research projects may / may not be conducted; or,*
4. *A research data registry from which future research may / may not be conducted.*

It is acknowledged that on submission, not all project methodologies may be known, but will evolve throughout the lifespan of the project.

Examples of a Program include, but are not limited to:

- A Principal Investigator identifies a research question and independent aspects of that question will be investigated by a series of research students as part of their Independent Learning Projects (ILP).
- There exists a common methodology, for example, a standard genetic test being used to address independent research questions across multiple disciplines.

- A longitudinal project that will develop over a number of years using different cohorts and research methodologies.
- A longitudinal project that will be replicated over a number of years across different cohorts.

5.5 Quality Improvement Activities

A Quality Improvement Activity is an activity where the primary purpose is to monitor, evaluate or improve the quality of health care by a health care provider. Improvement activities follow various methodologies but the basic principles are the same, making decision based on data and evaluating changes to ensure they are successful and sustainable.

Some Improvement Activities can be considered research some research studies may result in an improvement process.

Quality Improvement Activities are reviewed by the Clinical Governance Unit (CGU) and documented through the CHARLI database.

5.6 Other Applications Reviewed by the Research Ethics Office

5.6.1 Authorised Prescribers

An Authorised Prescriber application is one where a patient may require access to medicines or medical devices that have not been approved for supply by the Therapeutic Goods Administration (TGA). In such circumstances a medical practitioner may be granted temporary authority to become an Authorised Prescriber of such a product for a particular medical condition.

To become an Authorised Prescriber the medical practitioner must have:

- The training and expertise appropriate for the condition being treated and the proposed use of the product;
- The Authorised Prescriber must be able to best determine the needs of the patient; and,
- To monitor the outcome of therapy.

When completing an application for Authorised Prescriber with the TGA, applicants will require a letter of endorsement from the Human Research Ethics Committee. This can be obtained by submitting a copy of your TGA Authorised Prescriber application with a covering letter to the Research Ethics Office via email (SCHN-Ethics@health.nsw.gov.au).

The application should, at a minimum, include the following information:

- Indication – Disease to be treated;
- Clinical Justification – An outline of the seriousness of the condition, and, if other approved treatments are available, justification for the use of the unapproved product in preference to those treatments;
- Product Details;
- Administration and Monitoring Regime – Dosage, route of administration, duration of treatment, details of, and proposed monitoring;

- Efficacy and safety data

6 Submission & Review Processes

All submissions and correspondence must be sent from a valid email address linked to the contact person's organisation. Hotmail, gmail or TPG email addresses for example, will not be accepted.

6.1 Low / Negligible Risk Applications

6.1.1 Low Risk Applications

Applications for **low risk** research are reviewed by the Executive Committee. The Executive Committee comprises at a minimum, the Chair and the Executive Officer or their delegates. Wider membership includes: one member of the Scientific Advisory Committee (SAC), one lay member of the Human Research Ethics Committee (HREC) and one institutional member of the HREC.

The Executive Committee meets fortnightly to review applications.

6.1.2 Minimum Standards for Low Risk LNR Submissions

Low Risk LNR Submissions must be accompanied by the following documentation on submission:

- Low / Negligible Risk application form – completed online at www.ethicsform.org/au, downloaded and emailed as an original PDF (i.e. not scanned)
    - For LNR applications being submitted as part of the National Mutual Acceptance scheme, please refer to Section 6.2 below
- Project Plan of no more than five (5) pages
- Master Participant Information Sheet and Consent Form
- Master Parent Information Sheet and Consent Form
- **All** Research Tools that will be used (for example, questionnaires, focus group questions, surveys)
- **All** advertising material
- Invoicing Authorisation Form – **Commercial & Collaborative Group and Commercially Sponsored Studies**

6.1.3 Phase IV Clinical Trials and Post Market Observation Studies

Phase IV Clinical Trials and Post-Market Observation studies may be submitted as an LNR and reviewed by the Executive Committee. If the study is being reviewed under the National Mutual Acceptance Scheme, a NEAF will need to be completed, but the Executive Committee can be nominated as the reviewing authority.

6.1.4 Negligible Risk Applications

Applications for **negligible risk** research are delegated to the Executive Officer to review on a weekly basis.

Negligible Risk research projects will most typically involve projects that have no patient contact; i.e. medical records reviews.

6.1.5 Minimum Standards for Negligible Risk LNR Applications

Negligible Risk LNR applications must be accompanied by the following documentation on submission:

- Low / Negligible Risk application form – completed online at www.ethicsform.org/au, downloaded and emailed as an original PDF (i.e. not scanned)
    - Please Note – For all medical records reviews, Section 7.1 must be selected as "Yes" to "State / Territory"
    - For LNR applications being submitted as part of the National Mutual Acceptance scheme, please refer to Section 6.2 below
- Invoicing Authorisation Form –**Commercial & Collaborative Group Sponsored Studies**

6.1.6 Submission Process for LNR Applications

All LNR Applications are to be submitted electronically by COB the Tuesday of the week prior to the advertised Executive Committee review date. For Negligible Risk Applications the submission closing date is COB every Thursday.

Applications that do not meet the minimum standards will not be accepted for review.

An email acknowledging receipt of the application along with the date of review will be sent to the Principal Investigator and Contact Person within 48 hours of receipt.

For applications requiring review by the Executive Committee, the primary contact during the pre-approval process for Investigators will be the **Research Ethics Support Officer**.

6.2 Low Risk Applications under National Mutual Acceptance

In December 2015, the Office for Health and Medical Research Council provided guidelines for the expansion of the National Mutual Acceptance scheme to include Low and Negligible Risk Research.

Applications for low / negligible risk research being submitted through the National Mutual Acceptance scheme must be submitted on a NEAF, however will be reviewed through the wider membership of the Executive Committee, as agreed by the APREG (Australian Paediatric Research Ethics and Governance) Network.

6.3 National Ethics Application Form (NEAF) Submissions

PLEASE NOTE – This Section relates to applications to be reviewed by the full Human Research Ethics Committee. For low / negligible risk applications being submitted under the NMA scheme on a NEAF, please follow the guidance provided for LNR applications above.

Applications for review of **NEAF** submissions are reviewed by the Scientific Advisory Committee and Human Research Ethics Committee who meet on consecutive days, the third week of each month.

6.3.1 Minimum Standards for NEAF Applications

NOTE – Protocols must be endorsed by the Scientific Advisory Committee Primary and Secondary Reviewers prior to submission (please see Section 6.3.2).

NEAF applications must be accompanied with the following supporting documentation on submission:

- National Ethics Application Form (NEAF) – completed online at www.ethicsform.org/au, downloaded and emailed as an original PDF (i.e. not scanned)
- Protocol – Drug / Non-Drug – For Non-Commercial Trials on the templates available on the SCHN Intra-/Inter-net Page
- Investigator Brochure (if applicable)
- Master Participant Information Sheet and Consent Form
- Master Parent Information Sheet and Consent Form
- **All** Research Tools that will be used (for example, questionnaires, focus group questions, surveys)
- **All** Advertising Materials that will be used
- For applications involving radiation in excess of Clinical Care, a report from the Radiation Safety Officer at the Sites within the SCHN at which the study will be conducted.
- Invoicing Authorisation Form – **Commercial & Collaborative Group Sponsored Studies**
- Submission Checklist

6.3.2 Scientific / Peer Review Process

Scientific review through the SAC is achieved through Investigators submitting a 'Notice of Intention to Submit' and Invoicing Authorisation form to the Research Ethics Office at any time. Upon receipt, the Research Ethics Officer will coordinate for a 'Primary' and 'Secondary' Scientific Advisory Committee member to liaise with the Principal Investigator or delegate to pre-review the Protocol and provide a written endorsement to the Research Ethics Office prior to submission of the NEAF documents.

Investigators **must** be available, or delegate responsibility to an informed person, to discuss their protocol with the Primary and Secondary reviewers when submitting a 'Notice of Intention to Submit' (the 'Notice'). Where a contact person is not available, the Notice will be withdrawn and Investigators required to resubmit at a later stage.

Where the Primary Reviewer does not endorse the application to be reviewed by the HREC, it will not progress to the next available SAC meeting pending the closing date for submissions. It is the **responsibility of the Investigator** to ensure that all enquiries of the Primary and / or Secondary Reviewer are addressed before the Submission Closing date for the meeting.

All discussions that occur between the Primary Reviewer and the Investigator prior to the Submission Closing date and submission of NEAF documents must remain between the Investigator and Reviewers. The Research Ethics Office **will not** act as a conduit between the two parties for communication.

When the Primary and Secondary Reviewer are prepared to endorse the protocol, they will provide the Research Ethics Office with their report and pending receipt of the NEAF and supporting documentation from the Investigator, it will be listed at the next open scheduled Scientific Advisory Committee meeting and Human Research Ethics Committee meeting.

6.3.3 Submission Process for NEAFs

Subject to satisfactory outcomes of the scientific pre-review (as per section 6.3.2 above) process, all NEAF applications are to be submitted electronically by COB on the advertised Submission Closing date. Applications that do not meet the minimum standards will not be accepted for review. The NEAF Submission Checklist must be completed and included, along with all mandatory documents plus other documents supporting the project.

For applications requiring review by the full Human Research Ethics Committee, the primary contact during the pre-approval process for Investigators will be the **Research Ethics Officer**.

6.4 Declaration Signatures Required for Submission

When submitting an LNR or NEAF, the application form **must** be electronically signed (please refer to Section 6.5 below) by the following persons:

- Coordinating Principal Investigator (Principal Investigator for single site)

The Research Ethics Office **must** receive the signature of the following personnel by the time of the first review meeting.

- Head of Department
- All other SCHN Principal Investigators

If the signature of the Head of Department is not received within this time frame, the Research Ethics Office will not issue a feedback / approval letter until such time that it is received.

6.5 Electronic Signatures

This section should be read in conjunction with policy *Electronic Signing of Research Ethics Applications (LNR and NEAF)*.

The SCHN Research Ethics Office accepts electronic signatures for the submission of NEAF and LNR applications. When submitting an ethics application, investigators should nominate in the covering email the form of electronic signature used.

6.5.1 Forms of Electronic Signatures

The Research Ethics Office will accept the following forms of electronic signature when submitting a NEAF or LNR Application.

Please Note – The Research Governance Office may have alternative forms of electronic signatures and the SCHN Procedure *"Electronic Signing of Research Governance site specific applications: LNRSSAs"* (0/A/15:9083-01:00) should be referred to in that instance.

Online Forms generated

The Online Forms website has the capacity to sign LNR and NEAF declaration forms electronically by sending a request for authorisation via e-mail to the designated authority.

To obtain electronic authorisation, detailed instructions can be obtained through the following link which demonstrates a step-by-step guide:
https://au.ethicsform.org/Help/Demos/DemoElectronicAuthorisations.aspx

Adobe Signed Forms

For local PDF Forms (i.e. Annual Reports, Amendment Forms, Safety Reports etc) these can be signed using Adobe Reader tools.

To obtain an electronic signature:

- A signatory can insert a digital signature using the Adobe Rader Tab "Sign" followed by selecting "Place Signature"

Email of Signing Party Copied into Electronic Submission

If a person required to sign the LNR / NEAF is not able to electronically sign the document using one of the methods above, the person submitting the application should 'cc' those persons into the submission.

The signing party should then **reply all** to that email confirming their acceptance of the submission. Replies sent on that persons behalf will not be accepted (i.e. an Executive Assistant sending on behalf of the Head of Department).

Scanned Handwritten Signature

Handwritten signatures can be scanned and emailed with submission. Please do not scan the whole LNR or NEAF, only the signature page. Submission Codes and reference dates appear on each page of the LNR / NEAF and the Research Ethics Office will therefore be able to ensure that the scanned page relates to a particular submission.

6.6 Programs of Research Submission and Review

For Programs of Research scientific review may or may not be required, dependent on the type of program and how individual sub-projects will be managed. Advice must be sought from the Executive Officer in any instance ahead of intended submission.

A Program of Research must be submitted on a NEAF with the following supporting documentation:

- Master Protocol
    - For bio-banks and registries, the Protocol should also include sample / data collection and consenting processes.

- Terms of Reference (for certain Programs of Research only)
    - The Terms of Reference should be established to outline the obligations of each of the parties involved (e.g. the Program Principal Investigators and the sub-project Principal Investigator) including, but not limited to, the use of the Master Protocol, Participant Information Sheets and Consent Forms, annual reporting requirements, data custodians and authorship.
    - Terms of Reference should also be established for bio-bank and data registry review Committees.
- 'Access' Governance Procedures
    - For Bio-Banks and Registries, access protocols for obtaining samples / data from the bank / registry is required.
    - Included within this must be a condition that evidence of ethics approval from the applicant's local site will be provided when applying to access samples / data.
- Master Participant Information Sheet and Consent Form
- Master Parent Information Sheet and Consent Form
- Any other supporting material relevant to the ethical review of an application including, but not limited to:
    - Questionnaires
    - Surveys
    - Focus Group Questions
    - Invitation Letters
    - Advertising Materials

6.6.1 Sub-Project Approvals

Sub-projects are to be submitted on the '*Program of Research – Sub-Project Application*' Form. This form is a shortened version of the LNR and site specific.

Sub-project applications must have demonstrated authorisation from the Principal Investigator, Program of Research before submission to the Research Ethics Office.

Applications for sub-project approval will be processed as an **amendment** to the Program approval and resulting reference numbers will be, for example, "**HREC/16/SCHN/1/AM1**".

Sub-project applications will be reviewed by the Executive Committee.

7 Fees for Review of Research Ethics Applications

The NSW Ministry of Health has established minimum fees for the review of Research Ethics applications by the Human Research Ethics Committee. In accordance with this Policy Directive, the SCHN Research Ethics Office has established fees for these, and other types of ethics applications as deemed appropriate to ensure maintained service delivery.

Fees are payable on submission of an application (commencing with the 'Notice of Intention to Submit' process) with the option to request an invoice for payment. Applications where fee

payment is not received by time of first meeting review, will not have feedback issued until such time that the invoice has been paid.

The fees for review of research ethics applications and associated processes are:

Type of Application	Sponsor / Financial Support	Fee (GST Inclusive)
Application for Research Project (any form):	Full Commercial / Industry Funding	$3,300.00
Application for Research Project (any form):	Partial Commercial / Industry Funding	0.5% of total (funding) contract value up to $3,300
Application for Research Project (any form):	Collaborative Group Sponsored / Funded	$165.00 Non-GST Amount - $150.00
Amendments to Research Projects:	Full Commercial / Industry Funding	$550.00
Amendments to Research Projects	Collaborative Group Sponsored / Funded	$50.00
Addition of Sub-Studies to Research Projects[1]	Full Commercial / Industry Funding	$1,665.00

1. This includes sub-projects that are submitted under a Program of Research

Amendment fees for minor administrative changes, for example, addition of investigators, extension of time or sites, will not be subject to a review fee, irrespective of the source of funding.

If you are unsure of whether your application / amendment requires payment of a review fee, please contact the Research Ethics Office to discuss.

8 CTN / CTX Schemes

Clinical trials of unapproved therapeutic goods can be conducted in Australia under either the Clinical Trial Notification (CTN) Scheme, or the Clinical Trial Exemption (CTX) Scheme.

A CTN or CTX is required for:

- Any medicine or device not entered on the Australian Register of Therapeutic Goods (ARTG), including any new formulation of an existing product or any new route of administration; or,
- The use of a registered medicine or device beyond the conditions of its marketing approval, including new indications extending the use of the project to a new population group and the extension of doses or duration of treatments outside the approved range.

Clinical Trials Notification (CTN) Scheme

Under a CTN, all material relating to the proposed trial, including the trial protocol is submitted directly to the HREC by the researcher at the request of the sponsor. The Therapeutic Goods Association (TGA) does not review any data relating to the clinical trial and the HREC is responsible for ensuring that there is an assessment of scientific validity of the trial design and the safety and efficacy of the medicine or device as well as the ethical acceptability of the trial process.

As of 1 July 2015, the TGA will no longer accept the Clinical Trial Notification (CTN) forms in hard copy. This process will be entirely managed through online submissions. Processes have been established to enable the transition to the new electronic system.

Commercial and Collaborative Group Sponsored Studies

- It is the Sponsor's responsibility to draft and submit the CTN upon receipt of all approvals. No signatures are required.
- We will provide a factsheet, with SCHN HREC and site details, on our internet page to assist Sponsors completing their CTN form.
- A hard copy CTN is no longer required for these studies.
- Upon receipt of SCHN site authorisation, the commercial (or collaborative group sponsor) will submit their CTN electronically to the TGA

Investigator-Initiated Studies where SCHN is Study Sponsor

- Please continue to submit a hard copy of the CTN form to the SCHN HREC and Research Governance Office. A blank CTN form will be available on the SCHN Research Governance Intranet page.
- We have set up a SCHN TGA electronic account to allow electronic submissions of our CTNs. The SCHN Director of Research is the Administrator of this account.
- Upon receipt of site authorisation, the Research Governance Office will submit CTNs on behalf of SCHN. The Research Governance Office will request the Principle Investigator or Study Coordinator to make an appointment to facilitate the electronic lodgement of the CTN.
- During this transition period we will establish a list of SCHN Investigators who will be able to draft CTNs electronically through the TGA account. This will enable SCHN investigators to draft (but not submit) their own electronic CTN.
- No SCHN employee should set up a TGA e-account for their studies. If you have a CTN requiring lodgement or have previously set up a TGA ID / e-account please arrange an appointment with SCHN Research Governance: governance.schn@health.nsw.gov.au

Clinical Trials Exemption (CTX) Scheme

Under the CTX Scheme, a sponsor submits an application to conduct clinical trials to the TGA for evaluation and comment. In the case of clinical trials of medicines, the TGA reviews the information about the product provided by the sponsor, including the overseas status of the medicine, proposed Usage Guidelines, a pharmaceutical data sheet, a summary of the preclinical data and clinical data. For medical device trials the TGA examines the design specifications and preclinical data.

The TGA Delegate decides whether or not to object to the proposed Usage Guidelines for the product. If an objection is raised, trials may not proceed until the objection has been addressed to the Delegate's satisfaction. Even if no objection is raised, the Delegate usually provides comments on the accuracy and interpretation of the summary information supplied by the Sponsor. The Sponsor must forward these comments to the HREC(s) at sites which the Sponsor intends to conduct trials under the CTX.

A Sponsor cannot commence a CTX trial until:

- Written advice has been received from the TGA regarding the CTX application; and,
- Approval for the conduct of the trial has been obtained from an ethics committee and the institution at which the trial will be conducted.

9 Participant Information Sheets and Consent Forms

For any research involving contact with human participants, a Participant Information Sheet and Consent Form (PISCF) is required. Such forms are provided to potential research participants to aid understanding and describe, in lay language, what participation by the research subject will entail, the risks, costs, potential benefits and any other information that is likely to be material to a participant's consent. Any questions and concerns that the participant has should be addressed before they sign the Consent Form.

When developing a PISCF, the information should be presented in ways suitable to each participant. Further, consent does not necessarily mean signing a piece of paper and can also be expressed orally or implied, for example through completion of a survey, depending on:

i. The nature, complexity and level of risk of the research; and,

ii. The participant's personal and cultural circumstances.

It is ideal to include young persons in the consenting process, however, distinct from consenting to medical treatment in Australia, due to the ambiguity of Australian legislation related to medical research consent, it is a requirement of the SCHN HREC that the consent of all research participants under the age of 18 years be underpinned by that of their parents or legal guardian before any research-related procedures can be carried out.

Investigators are required to submit a **Master Participant Information Sheet and Consent Form** to the Research Ethics Office for review only. Site Specific Participant Information Sheets and Consent Forms are to be submitted to the Research Governance Office at each site at which the research will be conducted.

Note – Parental consent may be waived if specific exemption has been obtained from the lead HREC, in accordance with Section 4.2.9 of the *National Statement on Ethical Conduct in Human Research.* Researchers applying for exemption under this Section of the National Statement must provide the HREC when making such an application with reasonable justification.

The Australian Paediatric Research Ethics & Governance (APREG) Network in 2016 will release guidelines concerning the involvement of children in the consenting process. In essence, the following should be followed:

1. Children deemed to have the requisite maturity / capacity to understand should be provided with a Participant Information Sheet and asked to provide written consent by co-signing the Parent Consent Form.

   In determining capacity, researchers should ensure that their HREC application addresses:

   i. How the researcher will judge the child's vulnerability and capacity to provide consent;

   ii. Describe the form of proposed discussions with the child about the research and its effects at their level of comprehension; and,

   iii. Demonstrate that the requirements of Chapter 4.2 of the *National Statement* will be satisfied.

2. Children should receive age appropriate information about the proposed research study, in particular, of any risks or benefits of the study. Researchers should do so advising the child that they want the child's perspective on participating in the study.

3. Children, parents and / or guardians and other family members impacted by a child's participation in a research study should be involved in the conversation and reach consensus about participating in the study.

4. Researchers should recognise a child's developing capacity to understand and the fact that their maturity will develop throughout the research study. Age appropriate information should be provided throughout the study.

5. Confirmation of the appropriate completion of the consenting process must be written into the patient or study notes by the person performing the consenting process. At a minimum, this confirmation should confirm the date of the consent, the process of consent and a copy of the fully signed consent form that has been given to the parent and / or guardians.

6. If during the course of the study the child participant reaches the age of 18 years, the participant should be approached to re-consent on their own behalf to continue their participation at the earliest opportunity possible. The participant should be involved to consent to continuing participation (re-consent) by signing the currently approved Parent PISCF and the process should be documented as above.

The SCHN Human Research Ethics Committee recommends the following as a guide for developing Information Sheets, noting that Investigators should at all times take into consideration the type of study and the capacity of the child participant. It should be noted that fixed ages are not assigned to the type of Participant Information Sheet as this will vary depending on the study and capacity of the child:

Information Sheet	Guidance	Consent
Child / Young Person Information Sheet	This should be used in situations where the child has the capacity to be involved in the discussion on participating.	Not required but where possible it is recommended that the child participant co-sign the Parent Consent Form.

	A shortened version of the Participant Information Sheet in simple language and easy to read lay out	
Participant Information Sheet	For most studies where the Child is 16 years or more and has no cognitive or mental illness that prevents them from having the capacity to understand the research nature and demands. The content should be the same as that of the Parent Information Sheet replacing "your child" with "you"	All persons 16 - 18 years who do not have any cognitive or mental illness preventing them from understanding the nature and demands of the research should co-sign the Parent Consent Form.
Parent Information Sheet	For all studies where the research participants are under the age of 18 years.	Consent must be obtained for all research participants.

Assent

If a child does not have the requisite capacity or maturity at the time of the initial consent process or throughout the study, they should be provided with information and an opportunity to express their view about their involvement. Assent is an appropriate term to describe a child's (who does not have the requisite capacity) agreement to participate in a research study. The term assent however has no legal standing in Australia and is not a term recognised in the *National Statement*. It is a term used in law regarding medical research overseas.

Minimum Requirements for an Information Sheet

The *National Statement on Ethical Conduct in Human Research*, Section 2.2.6 outlines the minimum requirements for information to be contained within an Information Sheet. This includes:

- Any alternatives to participation;
- How the research will be monitored;
- Provision of services to participants adversely affected by the research;
- Contact details of a person to receive complaints;
- Contact details of the researchers;
- How privacy and confidentiality will be protected;

- The participant's right to withdraw from further participation at any stage, along with any implications of withdrawal, and whether it will be possible to withdraw data;
- The amounts and sources of funding for the research;
- Financial or other relevant declarations of interests of researchers, sponsors or institutions;
- Any payments to participants;
- The likelihood and form of dissemination of the research results, including publication;
- Any expected benefits to the wider community;
- Any other relevant information, including research-specific information required under other chapters of this National Statement.

Sample templates for Information Sheets are available on the SCHN Research Ethics Intranet page.

9.1.1 Research Ethics Office Review of PISCFs

On submission of an application to be reviewed by the full Committee, the Executive Officer will review the Participant Information Sheet and Consent Form for language and grammar and to ensure that the information contained accurately reflects the study protocol.

Ahead of the scheduled review date, the Research Ethics Office will send these comments to the Principal Investigator or delegate to review and accept changes, or make additional revisions.

For applications reviewed by the Executive Committee, post-meeting, with the feedback on the LNR / protocol, a tracked change version of the PISCF may also be fed back to the PI or delegate if amendments are required.

On responding to the feedback, if the changes are accepted by the PI / delegate, please submit the tracked changed version with 'accepted' commented next to each revision, and a clean copy with updated version and date information.

10 Informed Consent Considerations

The HREC considers consenting process that involve both verbal and written consent being obtained, as well as requests for implied consent. When considering these requests, the HREC will refer to the *National Statement, Section 2.2.5*, in particular:

1. The nature, complexity and level of risk of the research; and,
2. The participant's personal and cultural circumstances.

10.1 Implied Consent

Implied consent literally means that the participant's conduct implies that they are willing to participate; for example, when a potential participant returns a completed survey or questionnaire.

10.2 Verbal Consent

Such an approach to consent is appropriate when some written information has been provided to the potential participant ahead of the conversation during which the person provides their consent to participate; for example, a mail out before a telephone interview. During the latter phase of the consenting process, the investigator should record details of how oral consent was obtained.

10.3 Waiver of Consent

Chapter 2.3 of the *National Statement* outlines conditions under which the HREC will consider a waiver of consent. These conditions are:

- Involvement in the research carries no more than low risk;
- The benefits from the research justify any risks of harm associated with not seeking consent;
- It is impracticable to obtain consent (due to quantity, age, accessibility of records, for example);
- There is no known or likely reason for thinking that participants would not have consented if they had been asked;
- There is sufficient protection of their privacy;
- There is an adequate plan to protect the confidentiality of the data;
- In case the results have significance for the participant's welfare there is, where practicable, a plan for making information arising from the research available to them;
- The possibility of commercial exploitation of derivatives of the data or tissues will not deprive the participants of any financial benefits to which they would be entitled;
- The waiver is not prohibited by State, federal or international law.

The SCHN HREC will consider waivers of consent when investigators are undertaken medical record reviews. All other requests for waiver must be made with justification provided on why it is unreasonable to obtain consent.

10.4 Opt-Out Consent

In May 2014, the NHMRC revised the *National Statement* to include an option for "opt-out" recruitment to low and negligible risk studies. Section 2.3.5 of the *National Statement* defines an opt-out approach as being where *"…participant recruitment to research may be appropriate when, unlike waiver, it is feasible to contact some or all of the participants, but where the project is of such scale and significance that using explicit consent is neither practical nor feasible".*

Section 2.3.6 requires that the HREC consider the following before approving an opt-out consent process:

- Involvement in the research carries no more than low risk to participants;
- The public interest in the proposed activity substantially outweighs the public interest in the protection of privacy;

- The data on outcomes generated by the research activity is likely to be compromised if the participant rate is not near complete, and the requirement for explicit consent would compromise the necessary level of participation;
- Reasonable attempts are made for all prospective participants to be provided with appropriate plain language information explaining the nature of the information to be collected, the purpose of collecting it, and the procedure to decline participation or withdraw from the research;
- A reasonable time period is allowed between the participant receiving such information and the use of their data so that an opportunity for them to withdraw is provided before the research begins;
- A mechanism for prospective participants to obtain further information and register their intention for non-participation is provided;
- The data collected will be managed and maintained in accordance with relevant security standards;
- There is a governance process in place that delineates specific responsibility for the project and for the appropriate management of the data;
- The opt-out approach is not prohibited by State, federal or international law.

In addition to the requirements of the *National Statement*, the SCHN Human Research Ethics Committee has additional requirements for researchers who intend on using an Opt-Out approach:

- A minimum of four (4) weeks between the time that the Participant Information Sheet was posted and the time in which a participant can “opt-out” is required (not withstanding their ability to withdraw post this date). This period should be extended by two (2) weeks during the December / January school holidays and one (1) week where any other school holiday period occurs during the opt-out period.
- A simultaneous ‘opt-in’ process be applied wherever practicable; that is, persons who are keen to participate can return a consent form to the Investigators within the opt-out period to reduce ‘down time’ of the investigators waiting on the opt-out period to expire.

Requests for opt-out will only be considered where there is sufficient justification for such a consenting process to be used and the research has significant public interest.

10.5 Re-consent at 18 years

When submitting an ethics application where participation in the research is likely to continue past the participant’s 18th birthday, investigators should include in the protocol a plan for re-consenting the participant on their 18th birthday.

Similarly, when establishing a bio-bank or data-registry, Investigators should ensure that processes are in place to re-consent the participant at the earliest opportunity closest to their 18th birthday and give them the opportunity to elect to withdraw their samples / information. For bio-banks in particular, re-consenting the participant at 18 years enables them to be provided with updated information concerning potential return of incidental and significant findings that may not have been envisioned when the sample was originally consented.

For bio-banks where the samples were collected some yeas ago, all reasonable attempts must be made to contact participants.

10.6 Withdrawal / Revocation of Consent

The SCHN Human Research Ethics Committee acknowledges that different types of studies have different conditions for a participant withdrawing their consent to participate.

Please consider the following when developing Participant Information Sheets and research protocols concerning the withdrawal of consent:

- From the date the withdrawal of consent is received, no further information is to be collected from the participant and / or their records.
- Wherever possible, identifiable information that has already been collected in non-clinical trial research should be removed from data collection and destroyed securely and appropriately.
- Where de-identified information has already been collected, in non-clinical trial research, participants should be informed that it cannot be removed from data collections.
- For a clinical trial, the following wording or similar should be included in the Participant Information Sheet:

  "If you/your child decide to withdraw from participation during the research project, the study doctor and study staff will not collect any additional personal information from you or your medical records. Personal information that has already been collected will be retained as part of the study to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the Sponsor up until the time of withdrawal will form part of the research project results. If you do not want them to do this, you must tell them before the participant joins the research project"

11 Post-Ethical Review (Pre-Approval)

Once an application has been reviewed by the HREC or its delegate one of three outcomes will be reached:

- Approved
  - The application is approved with the standard and any additional conditions. The Investigator must obtain Site Specific Authorisation through the Research Governance Office before commencing activity on the research project.
- Further Information Requested
  - The HREC or its delegate requires clarification on minor aspects of the application. Once satisfactorily received, the application will be received. Again, once approved, Site Specific Authorisation is required.
- Resubmission

- The HREC or its delegate requires significant clarification or amendment to the protocol before it can be reviewed for approval. The researchers will need to resubmit their entire application once those concerns have been addressed.

Who Reviews Further Information?

Where further information is requested, the response may be delegated to a sub-Committee of the HREC, the Chair or other Committee Member, or the Executive Officer for review. Depending on which Committee or person will review, please contact the Research Ethics Office regarding submission dates.

11.1 Responding to Requests for Further Information

11.1.1 Three (3) Month Reply Timeframe

Once an application has been reviewed and a feedback letter issued, Investigators have a maximum of three (3) months or two (2) HREC meetings, whichever is sooner, to respond to Committee.

The Research Ethics Office will send regular reminders (at least one (1) every month) to the Principal Investigator and contact. At the end of the three (3) month period, the Research Ethics Office will send a letter to the PI and Contact advising that the application will be withdrawn if no response is received within two (2) weeks.

Once an application has been withdrawn, the applicant will need to submit an entirely new application and undertake full review again.

11.1.2 How to Respond to the Committee's Request for Information

1. **Do Not** alter the LNR or NEAF;
2. In a separate cover letter, address each of the points listed in the letter from the Committee. Clearly identify what question the response relates to and reference where in the Protocol or other document the revision has occurred.
3. Provide a **track changed** and **clean copy** of the documents which have been amended, noting that version numbers and dates of amended documents should be updated.
4. In the covering email list **all** of the latest documents, including version number and dates that have been reviewed for this application. In a separate colour, highlight those which have been resubmitted and thus version and date changed.
5. Submit all responses electronically.

If you disagree with the Committee's evaluation of an issue, please raise this in the response, providing justification for the Committee to consider.

12 Approval Conditions

There are several standard conditions of approval attached to each application approval:

1. The Coordinating Investigator will immediately report anything which might warrant review of ethical approval of the project in accordance with the SCHN Safety Reporting for Clinical Trials policy *1/A/12:9061-01:01*
2. All proposed changes to the research protocol, including the conduct of the research, changes to site or personnel, or an extension to HREC approval, are to be provided to the HREC or its delegate for review before those changes can take effect.
3. The HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.
4. The Coordinating Investigator will provide an annual progress report to the HREC on the anniversary of the approval letter, and a final report on completion of the study.
5. If the project extends beyond the approval expiration date and the project is still actively recruiting, Investigators are required to submit a new application incorporating any amendments approved since initial approval within six (6) months of the approval expiring. If the project is no longer actively recruiting but in follow up or analysis, an amendment is to be submitted requesting an extension for twelve (12) month periods up to three (3) extensions.
6. In the event that a project has not commenced within twelve (12) months of approval, the project approval will be withdrawn by the Research Ethics Office. Investigators will need to resubmit the application for full review should they wish to continue the study.
7. **For LNR Applications concerning medical records reviews –** Approval is restricted to the research being conducted on the nominated medical records only. Contact with patients, parents / guardians or other family members is not permitted.

12.1.1 Approval Periods

- LNR applications are approved for a period of three (3) years
- NEAF applications are approved for a period of five (5) years
- Clinical Case Reports and LNR Applications for Medical Records Reviews are approved for a period of 12 months unless otherwise specified.

13 Post-Approval

13.1 Amendments

An **amendment** is any proposed change to the conduct of an approved research project. Such changes include, but are not limited to:

- Addition or removal of a Principal Investigator
- Changes to the Protocol – administrative or scientific
- Changes to Participant Groups – addition of a cohort, age range, gender etc.
- Changes to the **Master** Participant Information Sheet and Consent Form

- Changes to, including the addition of, research tools, i.e. surveys, questionnaires, interview questions

As noted in Section 12 above, a condition of approval is that any amendments be notified to the Research Ethics Office for review and approval by the SCHN HREC or delegate before implementation.

Investigators can notify the Research Ethics Office of amendments using the 'Amendment Form' available on the SCHN Intra- and Internet pages or by contacting the Research Ethics Office. Once completed, the form is to be submitted electronically.

Original signatures are not required. The name of the Principal Investigator (PI) is required in the signature space and the PI is required to be copied into the electronic submission.

Minor administrative amendments, for example the addition of a new Principal Investigator, a new site being added or an extension to the approval time, are delegated to the Executive Officer for review. The majority of all other amendments are reviewed by the Executive Committee.

Amendments may be referred to the HREC for review if they contain substantial changes to the protocol through inclusion of a drug / device or other high intervention treatment.

When submitting an Amendment Form, please ensure that sufficient information is available to the HREC reviewers so that an accurate assessment can be made. For any revisions to Participant Information Sheet and Consent Forms, or any other research materials, both tracked and clean versions of the document are to be submitted.

Changes to Associate Investigators

The Research Ethics Office does not require notification of a change to an Associate Investigator or "other personnel", e.g. pharmacists, however the Research Governance Office do.

As Associate Investigators can change frequently, when preparing Participant Information Sheets, it is recommended that the actual name of the Associate Investigator be left off the Master Information Sheet and included on the Site Specific Version only.

Fees for Amendment Review

Commercial and Collaborative Group sponsored studies are required to pay a fee for review of Amendments, excluding strictly administrative changes in accordance with the Policy *Fees for the Review of Ethics and Site Specific Assessment Applications (1/A/14:9044-01:01)*.

13.1.1 Approval Periods

- Amendments reviewed by the Executive Committee in 2015 were reviewed, on average, within 18 days (approximately 108 amendments reviewed).
- Amendments reviewed by the Executive Officer in 2015 were reviewed, on average, within 8 days (approximately 140 amendments reviewed)

13.2 Annual Progress and Final Reports

Approved ethics applications are required to submit a progress report annually on the date of the anniversary of their approval. A final report is to be submitted on closure of the study. For

NEAFs this is **five (5) years** from the date of approval, and for LNR applications, **three (3) years**.

For NEAF, Clinical Research LNRs, bio-banks and registries, the Annual / Final Report form can be located on the SCHN Intra- and Internet pages.

For LNR medical record reviews and clinical case reports, the 'Low / Negligible Risk Research Final Summary Form' should be completed on completion of the project, or the ethics approval expiry date, whichever comes sooner. .

The annual / final report is to be submitted electronically to SCHN-Ethics@health.nsw.gov.au.

Annual and Final reports are not 'approved' but simply 'noted' by the HREC. If any information provided is unclear, the SCHN HREC may request further information before it will be noted.

Annual / Final reports are reviewed by the Executive Committee of the SCHN at their fortnightly meetings.

13.3 Adverse Event and Safety Reporting

Conditions for reporting of Adverse Events are documented in the SCHN Policy *Safety Reporting for Clinical Trials (1/A1/12:9061-01:01).* This document outlines procedures for safety reporting in clinical trials to ensure compliance with current Australian legislation and Good Clinical Practices as described in the TGA Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 1 and the NHMRC *National Statement on Ethical Conduct in Human Research*.

It is the responsibility of the Investigators to capture and report all AEs identified in the protocol, including SAEs and SUSARs which occur at their site. When SCHN is sponsor for the trial, the investigator must comply with regulatory reporting requirements.

Adverse Event (Drug)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom or disease temporarily associated with the use of a medicinal (investigational / experimental) product, whether or not related to this product.

Serious Adverse Events – SAEs

Drug

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (an event / reaction in which the patient was at risk of death at the time of the event / reaction, not an event / reaction which hypothetically might have caused death if it were more severe);

- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability / incapacity;
- Is a congenital anomaly / birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood duscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Device

Any adverse medical occurrence that:

- Led to a death;
- Led to a serious deterioration in health of a patient user or other. This would include:
  - A life threatening illness or injury;
  - A permanent impairment of body function or permanent damage to a body structure;
  - A condition requiring hospitalisation of increase length of existing hospitalisation;
  - A condition requiring unnecessary medical or surgical intervention; or
  - Foetal distress, foetal death or a congenital abnormality / birth defect;
- Might have led to death or a serious deterioration in health had a suitable action or intervention not taken place. This includes:
  - A malfunction of a device such that it has to be modified or temporarily / permanently taken out of service; or
  - A factor (a deterioration in characteristics or performance) found on examination of the device.

Serious Unexpected Suspected Adverse Reactions – SUSARs

Drug

These are serious adverse events for which there is some degree of probability that the event is related to the investigational product, and unexpected. The causality assessment may be made after the data is unblended (by the Data Safety Monitoring Board – DSMB).

Note – Serious and Severe are not synonymous

***Severity** usually refers to the intensity of an event (e.g. mild, moderate or severe). The event itself however may be of relatively minor medical significance (such as severe headaches).*

***Seriousness** is based on a patient / event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness, not severity, forms the basis of regulatory reporting obligations.*

Device

An undesirable clinical occurrence in a subject considered to be device related and not listed in the device technical manuals (or not listed in the appropriate section on the Adverse Event case report form).

13.3.1 Timeframes for Reporting

Reporting of **AEs** and **ADEs** to the Sponsor is in accordance with the study protocol.

AEs **do not** need to be reported to the SCHN HREC only where there has been a change in the participant's status with respect to participation in the study.

SAEs must be reported to the Sponsor immediately (usually within 24 hours) in accordance with the study protocol and GCP.

Principal Investigators of the SCHN sites are responsible for expedited reporting of SUSARs and SUADEs that occur at their site to the approving HREC as soon as practicable.

When the SCHN HREC is the approving HREC, an individual summary adverse event reporting form should be submitted within 72 hours of the event occurring.

International events that do not affect the overall conduct of the study should be reported as a 'line listing'.

TGA Reporting Requirements and Forms

The Therapeutic Goods Administration (TGA) requires:

- Rapid reporting of individual SUSARs and SUADEs within seven (7) calendar days for:
  - Fatal an unexpected events occurring within Australia.
  - Life-threatening and unexpected events occurring within Australia.
- Reporting within 15 calendar days:
  - All other individual SUSARs and SUADEs that are not fatal or life-threatening occurring within Australia.
- International SUSARs are preferably amalgamated into a single report.

13.3.2 Bi-Annual Reporting – 'Line Listings'

At least once every six months for clinical trials of a therapeutic drug / device only, a list of all suspected unexpected serious adverse events / reactions, Australian and International, occurring within a compound or device including sponsor and Coordinating Investigator comments on planned action (if any) should be submitted to the Research Ethics Office electronically.

13.3.3 Annual Reporting – Safety Updates

At least annually the following documents / reports should be submitted for clinical trials of a therapeutic drug / device:

- Updated Investigators Brochure (IB), or
- A European Union Annual Safety Report (EU ASR) or similar format report, or
- Current, approved product information (PI), if appropriate.

13.4 Protocol Deviation / Violations

A **Protocol Deviation** is a minor or administrative departure 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 of Protocol Deviations include:

- Follow up visits that occurred outside the protocol required time frame because of the participant's schedule;
- Blood samples obtained at times close to but not precisely at the time points specified in the protocol.

In reporting Protocol Deviations, whilst the Principal Investigator may choose to submit a list of deviations for the HREC and / or its sub-committee to note, it is not a condition of the approval that such a list be submitted, unless it affects patient safety.

A **Protocol Violation** occurs in 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 of Protocol Violations include:

- Failure to obtain participant consent;
- Participant inclusion / exclusion violations.

A Protocol Violation should be reported as an adverse event to the Research Ethics Office as soon as possible after the event has occurred.

14 Pre-Submission Discussions with Research Ethics Office

The Research Ethics Office encourages researchers to discuss their application with a member of the team ahead of any submission where it is unclear whether a NEAF or LNR is required, there are complex ethical issues, or simply to understand the submission process better.

The Children's Hospital at Westmead

The Research Ethics Office is based at the Children's Hospital at Westmead and appointments can be made at any time by emailing SCHN-Ethics@health.nsw.gov.au or contacting 02 9845 1253 with your preferred date and time. Depending on the nature of the enquiry, the appointment may be made with one of the Research Ethics Officers or the Executive Officer.

Sydney Children's Hospital, Randwick

A member of the Research Ethics Office attends the Sydney Children's Hospital, Randwick every other Monday (please confirm with the Office dates) between 9am and 1.30pm to meet with researchers and discuss projects. Appointments must be made by researchers for these visits due to demand and ensuring that appropriate time can be spent with each person to

discuss their project. Appointments can be made by emailing SCHN-Ethics@health.nsw.gov.au or contacting 02 9845 1253. Appointments can be made in ½ hour blocks depending on the level of enquiry.

When making an appointment, please include some basic information about your enquiry / project so that we can ensure the best person is assigned to provide you with advice.

Disclaimer – Any information provided to Researchers by the Research Ethics Office is advice only and may not wholly represent the opinion of the Reviewer or HREC. Recommendations are provided based on previous ethical reviews, however each application is considered on its own merits.

15 Education and Training

The Research Ethics Office and the Research Governance Office both provide training and education opportunities for researchers. Please refer to the SCHN Intra- and Internet pages for the training schedule.

Individual Training Sessions

If you would like the Research Ethics Office to host an independent ethics training session for your department, or for a group of researchers, please contact the Research Ethics Office at SCHN-Ethics@health.nsw.gov.au or via telephone (02) 9845 1253 to arrange.

16 Ethical Issues to Consider when Preparing an Application

16.1 Withdrawal of Consent

Section 2.2.20 of the *National Statement* states that:

> *"Participants are entitled to withdraw from the research at any stage. Before consenting to involvement in the research, participants should be informed about the consequence of such withdrawal"*

Consequence may mean the following:

- For Clinical Interventional Research – How to safely withdraw from a clinical study involving a therapeutic drug and the relevant clinical implications of this, or alternative treatments available.
- For Non-Interventional / Health Research – What will happen to the person's data already collected if they elect to withdraw.

  Wherever possible, it is recommended that all identifiable data collected up until the point that the person withdraws be removed and destroyed.

  For data that is collected in a de-identified format, i.e. surveys, focus group discussions where a person cannot readily be identified, it should be made very clear in the Participant Information Sheet that such information will not be able to be removed.

16.2 Clinician / Researcher – Avoiding Coercion in Recruitment

Chapter 4.3 of the *National Statement* is concerned with research involving people in dependent or unequal relationships, including '*healthcare professionals and their patients or clients'*.

The Committee is concerned, in reviewing applications with ensuring that the clinical relationship that exists between clinician and patient does not impede on the potential researcher / participant relationship; that is, that the participant is not influenced by the researcher's position as their clinician to consent to participate in the research.

Wherever possible, the Committee would recommend that the clinician not be the person who makes the initial contact with the potential participant. It is acknowledged however that this is not always possible and that in some cases, for example Oncology trials, the clinician / researcher is the most appropriate person to introduce the study.

16.3 The 'Ick' Test

When reviewing ethics applications, it is the responsibility of the Committee, particularly the Community Members to put themselves in the participant / parent's shoes when considering whether the protocol is ethically acceptable, and the risks tolerable.

It is recommended that researchers also take this into consideration when designing their research protocol; i.e. ask yourself, "*Would I be happy for my family member of close friend to have 'x' extra blood draws per week for research purposes that will be of no benefit to them?"*

It is acknowledged that this is not always possible as to maintain scientific integrity there is a necessity to administer x number of blood tests or other invasive procedures. The Committee's position is more about thinking about what is the most minimally invasive way to achieve the same outcomes.

16.4 Information Sheets

Section 9 of this Guideline is concerned with when a Participant Information Sheet and Consent Form should be in place. Following are some suggestions on developing Information Sheets:

- **Keep it Simple.** The recommended reading level for a Participant Information Sheet for adolescents and adults is Grade 8; i.e. 13 years old. Microsoft Word has the capacity to provide you with a reading level of the document.
- **Avoid** the use of medical jargon. Even though your potential participants may be very knowledgeable about the disease / illness and understand what has been written, the document should be written in a way that can be understood by anyone.
- **Use tables** to illustrate the schedule of appointments. This will provide a clear visual to the potential participant of the commitment required of them during the study.
- **Highlight time commitment and be realistic**. The Committee has found that the majority of times a person withdraws from a study because they were unaware of just how much time they were required to commit to their participation. You should also be realistic in your estimation of how long something will take to complete.

- **There is always the potential for risk**. Risk is unavoidable in research, whether it be to health, physical or mental wellbeing, or even to privacy. In the majority of low risk research, the risk will be extremely low, but it is always best to acknowledge that whilst there are no foreseeable risks, there may be factors affecting a person's participation that may cause risk that the investigators are unaware of at the outset.
- **Risk Management Plans and Support Services.** Where there is a risk identified as a result of participation, the Information Sheet should clearly explain the protocols that are in place for managing it. This includes the provision of support services other than the researchers. Investigators should be mindful that when participants are sent surveys or questionnaires to complete, they may not complete them until the evenings or later at night when it is quiet. Should they become upset or distressed, it is more often the case than not that the researcher, or contact person, will not be available to talk through the study with the participant. Alternative contact persons should be available, or a 24 hour support line noted in the Information Sheet where there is a chance that the participant could become upset by their research involvement.
- **Sensitive research involvement.** The content of some validated questionnaires, particularly in psychological type studies, can be highly sensitive and intrusive; for example, it may ask about the participant's sex life or happiness in their marriage. If your survey / questionnaire contains any questions that may be considered highly sensitive, it is recommended that some examples of these questions be included in the Information Sheet. This would eliminate any wasted time of the researcher and the participant completing a study where their involvement is withdrawn.
- **Visual aids for younger children.** A PISCF is a useful tool to assist communications about the study between the researcher and the child participant; however it is not the only tool available. Videos, presentations, pictures, and YouTube clips are some ways that researchers can help explain the research study to the child participant.
- **Check spelling and grammar!** The Research Ethics Office spends a significant amount of time when reviewing Participant Information Sheet and Consent Forms reviewing spelling and grammar. To minimise delays in approving PISCFs, please ensure that you proof read and edit before submission.
- **Avoid the use of personal email and / or phone numbers as a contact**. The HREC discourages the use of personal email addresses or mobile phone numbers as the advertised contact for study complaints or further information. Should you get a disgruntled 'customer' this could pose a potential risk to the researcher by them having access to such information.

16.5 Document Version Control

All documents submitted (excluding the LNR / NEAF) must be Version Controlled using a "version number" and "date of version" format. Documents that do not have appropriate version control will not be accepted.

16.6 Privacy and Publication

The response provided in NEAF and LNR documents regarding privacy and publication have become standard, however do not always demonstrate a sufficient understanding of what it means to de-identify information so that privacy and confidentiality is not breached.

Researchers should be mindful of the following when designing their research to protect participant privacy and confidentiality that smaller cohorts have increased risk of identification. For rare diseases, there is a greater risk of persons being identifiable by nature of the specifics of their illness. Extra care should be taken by researchers when describing specifics of a person's illness in publication.

Some techniques to remove identifiers are as follows:

- Remove variables – For example - Ethnicity
- Recording –DOB to age ranges, i.e. 35 – 44 years old
- Suppression – Replace value with 'missing'
- Micro-aggregation – Group in fours, for example, i.e. ages 31, 33, 33 and 34 become 32.75
- Data-swapping – For example, swap salaries for two people within the same postcode so that the aggregate is not affected.
- Add noise, sampling, etc.

16.7 Recruitment Matters

When completing the NEAF, LNR and/or Protocol, researchers should be explicit in documenting their process for identifying and initially approaching potential participants.

Section 2.2.9 of the National Statement states that

> *"No persons should be subject to coercion or pressure in deciding whether to participate. Even where there is no overt coercion or pressure, consent might reflect deference to the researcher's perceived position of power, or to someone else's wishes. Here as always, a person should be included as a participant only if his or her consent is voluntary"*

Taking this into consideration and the potential for deference given the nature of the environment and type of research being undertaken, the Committee requests wherever possible that the following recruitment process be used:

1. For clinical research where the intention is to consent potential participants at the next clinic appointment, a letter of introduction / invitation to the study be sent to the participant ahead of the clinic appointment. This will enable the potential participant to consider whether they would like to participate or not before they are formally invited to participate and consent.
2. Where the intention is for researchers to approach potential participants in clinic waiting areas and it has not been possible to make contact ahead of their appointment, posters or other advertising materials should be placed in obvious locations throughout the clinic so that potential participants are aware of the study before they are approached.
3. Where the intention is to recruit in emergency or through wards, a third party who is familiar with the potential participant and / or their family, i.e. a nurse, must make the

initial contact with the family / participant to determine their level of interest in participation before introducing them to the researcher.

If this is the intended method of recruitment, the researcher must provide with their application to the Research Ethics Office a **letter of support** from the NUM or Head of Department that this is the process being used.

4. **Be sensitive and conscious of timing in recruitment.** Researchers should be ever mindful of the mental health of the potential participant / parent when initially approaching them to participate. Unless the timing of approach is critical to the outcomes of the study, potential participants should always be given the opportunity to consider the medical status of their child before being approached to participate in any study.

16.8 Terminology

Following are some appropriate terms to use when developing a protocol and preparing PISCFs:

- **Controls –** Control participants should be referred to as 'healthy' **not** 'normal'.
- **Patient / Participant –** For medical record reviews, the term 'patient' should be used. For all other research involving an actual interaction, the term 'participant' should be used.

17 Research Ethics Contact Details

The Research Ethics Office can be contacted between 8.00am and 4.30pm Monday to Friday via telephone at (02) 9845 1253, or anytime at SCHN-Ethics@health.nsw.gov.au.

Executive Officer

Please contact to discuss:

- Overall management of the Research Ethics Office and Committees
- Committee Membership
- Regulatory Reporting
- Complaints – conduct of research or committee review
- Complex projects / programs of research
- Policies and procedures
- Invoicing disputes

Research Ethics Officer

Please contact to discuss:

- Scientific Advisory Committee

- Human Research Ethics Committee
- General enquiries relating to ethical review.

Research Ethics Support Officer

Please contact to discuss:

- Executive Committee
- Post-approval – Amendments, annual reports, safety reports
- General enquiries relating to ethical review
- Committee Member newsflash

Research Ethics Administrative Assistant (Tuesday, Wednesday & Thursday)

Please contact to discuss:

- Negligible Risk research application
- Post-approval – Amendments
- General enquiries relating to ethical review
- Research Ethics Office newsletter
- Invoicing enquiries
- Meetings with the Research Ethics Office