CLINICAL TRIALS

POLICY©

DOCUMENT SUMMARY/KEY POINTS

All Clinical Trials performed at Sydney Children's Hospitals Network must comply with all aspects of current Legislation and Good Clinical Practice as described in the TGA Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 1.

- This document provides an overview of current policy and briefly summarises regulated procedures involved when conducting Clinical Research across Sydney Children's Hospitals Network (SCHN).

CHANGE SUMMARY

- SCHN Document rescinds CHW document 1/A/07:8346-01:02 of the same title
- There are many changes throughout the document including the restructure of some sections. For this reason, it is recommended to read the entire document.

READ ACKNOWLEDGEMENT

- All staff who are considering to undertake or who are involved with clinical trials at SCHN should read this document.

This document reflects what is currently regarded as safe practice. However, as in any clinical situation, there may be factors which cannot be covered by a single set of guidelines. This document does not replace the need for the application of clinical judgement to each individual presentation.

Approved by:	SCHN Policy Procedure & Guideline Committee	
Date Effective:	1st November 2014	**Review Period**: 3 years
Team Leader:	Manager	**Area/Dept**: Clinical Research Centre

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1 Commonly Used Abbreviations

Abbreviation	
ADEC	Adverse Drug Evaluation Committee
AE	Adverse Event
AHEC	Australian Health Ethics Committee
ADR	Adverse Drug Reaction
ADRAC	Adverse Drug Reaction Advisory Committee
ARCS	The Association of Regulatory and Clinical Scientists
ARTG	Australian Register of Therapeutic Goods
CDER	Centre for Drug Evaluation and Research
CHW	Children's Hospital at Westmead
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CTC	Clinical Trials Coordinator
CTN	Clinical Trials Notification
CTRA	Clinical Trials Research Agreement
CTX	Clinical Trials Exemption
DSMB	Data Safety Monitoring Board
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HREC	Human Research Ethics Committee
HSC	Health Services Commission
ICH	International Committee of Harmonisation
IB	Investigators Brochure
LNR	Low and Negligible Risk
NEAF	National Ethics Application Form
NHMRC	National Health and Medical Research Council
QA	Quality Assurance
SAE	Serious Adverse Event
SPT	Special Purpose & Trust (fund)
SCH	Sydney Children's Hospital
SCHN	Sydney Children's Hospitals Network
SSA	Site Specific Application form
TGA	Therapeutic Goods Administration
WHO	World Health Organisation

Hospital: The "Hospital" refers to The Children's Hospital at Westmead (CHW) and Sydney Children's Hospital (SCH).

2 Background

2.1 What is a trial?

A clinical trial is a form of human research designed to find out the effects of an intervention, including a treatment or diagnostic procedure. A clinical trial can involve testing a drug, a surgical procedure, other therapeutic procedures and devices, a preventive procedure, or a diagnostic device or procedure.

A clinical drug trial is any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.[2, 12]

The Clinical Research Centres at Sydney Children's Hospital (SCH) and Children's Hospital at Westmead (CHW) are a resource centre for all clinical investigators wishing to conduct a clinical trial at this site. The Sydney Children's Hospitals Network (SCHN) intranet page offers guidance documents and templates that can be downloaded and adapted for individual clinical trials.

2.2 Key Characteristics

Clinical Trials are conducted to:

- improve diagnostic, therapeutic or prophylactic procedures (Declaration of Helsinki[3])
- ensure treatment is efficacious with minimal side effects
- market drugs to benefit people

2.3 Types of Clinical Trials

Clinical trials of drugs are generally classified according to the stage of drug development.[4]

From the National Statement on Ethical Conduct in Human Research (2007), Chapter 3.3:

- **Phase I** studies involve the first administration of the medicine to humans. Medicines are usually given to small numbers of healthy volunteers, but sometimes to people affected by the disease the medicine is intended to treat. The purpose may be to determine the medicine's safety, pharmacokinetics, pharmacological activity, side effects, preferred routes of administration, or appropriate doses (for later studies). The studies are usually undertaken in centres equipped for specialised monitoring and a high degree of surveillance.
- **Phase II** studies are typically the first trials of the medicine in people with the health condition for which the medicine is intended. The principal aim is to determine efficacy and safety and establish an appropriate dosing regimen. These studies are undertaken in a small number of closely supervised patients and conducted by researchers regarded as specialists in the health condition and its treatment.

- **Phase III** studies are undertaken if the Phase II studies indicate the medicine has potential benefits that outweigh any hazards. The studies involve greater numbers of patients with the health condition under study, and aim to determine whether the medicine confers clinical benefit in that health condition and whether the incidence and nature of adverse effects are acceptable.
- **Phase IV** studies are those undertaken after the medicine has been approved for marketing for the treatment of a particular disease or for a particular indication. They may include studies to compare the medicine with a wider range of therapies, and may also further investigate the use of the medicine in the normal clinical setting of the disease (which may differ markedly from the conditions under which pre-marketing trials were conducted). Such studies also gather more comprehensive safety data, adding to the information known from the pre-marketing studies.
- In pharmaceutical and medical device trials there are established codes of good clinical research practice that define clearly what is meant by a clinical trial for those purposes (see the Australian code for the responsible conduct of clinical trials5). This chapter's main application is to biomedical clinical trials, but it also applies to any other interventions claiming therapeutic benefit. Trials involving experimentation with therapeutic goods, whether drugs or devices, that are not yet registered, listed or entered on the Australian Register of Therapeutic Goods (ARTG) are subject to regulation by the TGA.

3 Regulation of Clinical Trials

3.1 Regulation by the Therapeutic Goods Administration (TGA)

3.1.1 What does the TGA regulate?

Researchers at SCHN should familiarise themselves with the TGA regulations of clinical trials1 in Australia on the TGA website http://www.tga.gov.au/industry/clinical-trials.htm or contact them directly on 1800 020 653 for any specific questions.

The TGA regulates all clinical investigational use of a product/device in Australia, where that use involves:

- A product/device not entered on the Australian Register of Therapeutic Goods, including any new formulation of an existing product or any new route of administration; or
- Use of a registered or listed product/device outside the conditions of its marketing approval.

Clinical trials in which products/devices are used within the conditions of their marketing approval are not regulated by the TGA but will still need to be approved by a Human Research Ethics Committee (HREC) before the trial may commence. Approved indications appear in the product information sheet (MIMS or Pharmaceutical Company supplied); these are the only indications that have been approved by the TGA.

There are two main routes for conducting a clinical trial of a new therapeutic good or new uses of therapeutic goods; the Clinical Trial Exemption (CTX) Scheme and the Clinical Trial

Notification (CTN) Scheme, explained in sections below. The CTX Scheme is an approval process and the CTN Scheme is a notification process. Over 95% of all trials conducted in Australia obtain regulatory approval via the CTN scheme.

It is also important to remember that all therapeutic goods used in an unapproved manner in a clinical trial, not simply the main product of interest, are required to be noted on the CTN or CTX paperwork.1

If unsure, the HREC has delegation to determine whether a trial is to be considered under the CTN or CTX scheme. If unsure of the requirement for your trial you should contact the TGA directly.

A completed CTN or CTX form should be submitted with your ethics application for signing by the Chair upon approval by the HREC. A copy of the signed form will be provided to you with your approval letter. The signed CTN is then sent to the TGA by the Chief Investigator (or Study Sponsor if applicable) before the trial commences. All forms sent to the TGA must be signed originals.

3.1.2 How do you apply to the TGA for approval?

For comprehensive information regarding the CTN and CTX scheme, including detailed instructions on how to complete the respective forms, the document "Access to Unapproved Therapeutic Goods – Clinical Trials in Australia" should be consulted.[1,6]

3.1.3 Clinical Trial Notification (CTN) Scheme

The CTN form is available on the TGA website: http://www.tga.gov.au/industry/clinical-trials-forms-ctn.htm

Generally a CTN is appropriate for:

- Phase I and II studies if there is adequate preclinical data available and have been extensively reviewed overseas (e.g. FDA)
- Phase III and IV studies and bioavailability/bioequivalence studies of medicines
- Extensions to trials previously under the CTX Scheme

The TGA does not review any data relating to the clinical trial if applying via the CTN Scheme. The HREC is responsible for assessing the scientific validity of the trial design, the safety and efficacy of the medicine or device and the ethical acceptability of the trial process, and for approval of the trial protocol.6

Following HREC approval the coordinating investigator (or the Sponsor if applicable) sends the completed CTN form, signed by the HREC (and fee) to the TGA. Once these have been lodged, the investigator does not need to wait for the acknowledgment letter to begin the trial, although the investigator or sponsor should keep evidence of postal lodgement to the TGA.

From 01 July 2014, the CTN notification fee is $330 per notification. This fee rises each year on 01 July. For current fees, visit: http://www.tga.gov.au/about/fees.htm. It is preferred if all sites participating in the trial are notified either simultaneously or in groups as per fee structure below:

Sites	Fees
All sites notified at the same time (including composite sites)	Single notification fee
Each site notified singly	Notification fee for each separate notification
Sites notified in groups	Notification fee for notification of each group

At trial completion the TGA must also be notified: the notification form is available on the TGA website: http://www.tga.gov.au/industry/clinical-trials-forms-ctx.htm

3.1.4 Clinical Trial Exemption (CTX) Scheme

The CTX scheme is used where there is little or no information about a drug or device which is sought to be trialled. A CTX application offers investigators and sponsors the opportunity of a review by the TGA of relevant, but limited, scientific data (which may be preclinical and early clinical data) prior to the commencement of the trial. An application to conduct clinical trials is submitted to the TGA for evaluation and comment. A 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.

A trial cannot commence under the CTX scheme until:

- Written advice has been received from the TGA regarding the 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.

There are two forms, each reflecting these separate processes that must be submitted to the TGA.

- Part 1 constitutes the formal CTX application. It must be completed by the sponsor of the trial and submitted to TGA with data for evaluation (see: http://www.tga.gov.au/industry/clinical-trials-forms-ctx.htm).
- Following Ethics and Site Specific Approval Part 2 is used to notify the TGA of the commencement of the trial. The Part 2 form must be submitted within 28 days of the commencement of supply of goods under the CTX (see: http://www.tga.gov.au/industry/clinical-trials-forms-ctx.htm).

The fees for applications for clinical trials under the CTX scheme are significantly higher than under the CTN. This reflects the increased work required by TGA to evaluate the data provided. There is a single fee for the CTX that includes both Parts 1 and 2.

The TGA fee (as of 01 July 2014) for a CTX application is between $1595 and $19,900, depending on the complexity of the submission. For current fees, visit: http://www.tga.gov.au/about/fees.htm.

3.2 Regulation by the Human Research Ethics Committee (HREC)

3.2.1 What does the HREC Regulate?

The Sydney Children's Hospitals Network Human Research Ethics Committee (SCHN HREC) is responsible for ensuring the scientific and ethical acceptability of all clinical trials conducted across the Network by staff or students of the Hospital, or other stakeholders, which involves human participants, their tissue or identifiable information. It is also responsible for the provision of advice to the Research Executive on related matters.

3.2.2 How do you apply to the HREC for approval?

Prior to preparing their application, investigators should familiarise themselves with the NHMRC National Statement on Ethical Conduct in Human Research4 and the International standard of Good Clinical Practice (GCP) and the TGA Note for Guidance CPMP/ICH/135/95. Any investigator wishing to undertake a clinical trial should complete a Good Clinical Practice (GCP) workshop. You should contact the Clinical Research Centre staff at Randwick and Westmead for further details.

The policy "Fee for Review of Ethics and Site Specific Applications" is available on the intranet at both CHW and SCH. This outlines the requirement for payment to be made on submission for Ethical and Governance review.

Please ensure that you inform the pharmaceutical company (for industry sponsored trials) of these charges and/or it is provided for in the study budget.

The SCHN HREC requires the National Ethics Application Form (NEAF) be completed through the Online Forms (www.ethicsform.org/au) website and submitted as per the guidelines available on the Research page of the intranet.

All investigators should consult with the Research Ethics Office and Clinical Trials Pharmacist (if conducting a clinical drug trial) prior to preparing their application and note the NEAF submission dates.

All documents should be submitted to the SCH HREC Office by the advertised closing date.

A separate Scientific Protocol must be included in your application.

3.2.3 National Ethics Application Form (NEAF)

- SCHN HREC only accepts applications that have been completed through the Online Forms website, https://www.ethicsform.org/Au/Signin.aspx
- The NEAF is completed online and a submission code generated once finalised.
- The purpose of the NEAF is to provide an overview of the clinical trial to enable the HREC to make a determination of the ethical acceptability of the project in terms of risk and benefit to the participant and the wider community. The NEAF is by no means comprehensive enough to make a complete decision on this ethical acceptability researchers are required to submit a complete Protocol in support of the NEAF. Protocol templates are available on the SCHN Research Intranet Page.
- For further details on completing the NEAF, refer to The National Ethics Application Form Guidance Manual or NEAF Handbook found on the SCHN intranet.

3.2.4 Ethics Approval Process

- All clinical trials conducted with the Network must have approval from the SCHN HREC or another lead HREC certified for the review of paediatric clinical trials, as well as Site Specific Authorisation from the Research Governance Office before commencing.
- Following submission of the Application, two (three if required) reviews will take place:

  i. **Scientific Advisory Committee Review**
  All clinical trials will be reviewed by the Scientific Advisory Committee to ensure scientific validity of an application.

  ii. **Human Research Ethics Committee Review**
  Once determined to be scientifically approved, applications will be reviewed by the Human Research Ethics Committee for ethical approval.

  Please note that some applications will require review prior to the scientific / ethical review by the Drug Committee

  All clinical drug trials will require review by the Drug Committee in addition to Ethical and Scientific Review. It is the responsibility of the CHW PI to ensure their clinical trial is submitted to the CHW Drug Committee for review. This review is conducted by the Drug Committee at its meeting and the review is independent of the SCHN HREC or other certified HREC. On occasions, the Drug Committee will consider protocols after they have been considered by and possibly approved by the HREC.

  Sponsors should comply with NSW Ministry of Health Policy Directive (PD2005_078): Drugs - Highly Specialised Program - Guidelines for Undertaking Clinical Trials[10]
- Investigators should allow approximately 2 months for approval from the date of submission.
- At each stage of the review process, the Research Ethics Office will issue a letter advising scientific and ethical approval of the application. A Drug Committee approval letter must be sent to the Research Governance Office at the time of your submission or as soon as it becomes available.
- The Research Governance Office will require drug committee approval for all clinical drug trials approved by all HRECs in NSW and other states under the Mutual Acceptance scheme.

3.2.5 Conditions of HREC Approval of clinical trials

HREC approval is subject to the following standard clauses:

- The Co-ordinating investigator will immediately report anything which may warrant review of ethical approval of the project in the specified format, including:
  - Unforeseen events that might affect continued ethical acceptability of the project,
- Proposed changes to the clinical trial protocol, conduct of the clinical trial, or length of HREC approval, will be provided to the HREC for review in the specific format.
- The HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.

- The coordinating investigator will provide an annual report to the HREC and at completion of the study.
- Your approval is valid for 5 years from the date of the final approval letter. If your project extends beyond five years then at the 5th year anniversary you are required to resubmit your protocol, according to the latest guidelines, seeking the renewal of your previous approval. In the event of a project not having commenced within 12 months of its approval, the approval will lapse and reapplication to the HREC will be required.

The SCHN HREC reserves the right to add project specific conditions to any application reviewed for ethics approval.

3.3 Regulation by Research Governance

3.3.1 What does Research Governance regulate?

The Research Governance office regulates the conduct of all types of research activity on any site under SCHN by giving site authorisation to conduct a clinical trial at SCHN. This is called Site Specific Approval. The Site Specific Application will be reviewed by the Research Governance Office.

For all NEAF SSAs, the Director of Research will grant Site Specific Approval upon recommendation of the Research Governance Office.

For all LNR SSAs, the Research Governance Manager of Officers has delegation to grant Site Specific Approval.

3.3.2 How do you apply to SCHN Research Governance for Approval?

- The SCHN Research Governance requires the Site Specific Authorisation (SSA) Form to be completed which is accessed online and linked to the NEAF
- Submit the SSA and all accompanying documents to the Research Governance Office. The SSA can be submitted in parallel with your ethics application but separately to the Research Ethics Office
- For further details on documents required for submission, please go to the Research section of the SCHN intranet: http://intranet.schn.health.nsw.gov.au/research

3.3.3 Site Specific Application (SSA) Form

- All investigators are required to complete the Site Specific Authorisation (SSA) Form to request approval to conduct their clinical trial at the Hospital. This is linked to the online NEAF application and accessed via the NEAF website: https://www.ethicsform.org/Au/Signin.aspx
- Many fields on the SSA will be automatically populated from the NEAF.

3.3.4 Additional Research Governance Submission Requirements

Often trials are initiated by a commercial company or some other organisation who becomes the “external sponsor of the trial.” Additional documentation to be submitted with the Site Specific Application for sponsored trials includes:

1. **Clinical Trial Research Agreement (CTRA)**
    - This is an agreement between the study Sponsor, the Hospital (The Sydney Children's Hospitals Network (Randwick and at Westmead) (incorporating The Royal Alexandra Hospital for Children). Where possible the investigator should negotiate directly with the Sponsor regarding any alterations to the Agreement. Please contact the Research Governance Office if you require assistance. The entity names and details required for the CTRA can be located in the Research Agreement/Contract Instruction Sheet in the Governance section on the SCHN intranet: http://intranet.schn.health.nsw.gov.au/research
    - All clinical drug and device trials at SCHN must have Schedule 2 (Payments) as an attachment to the Clinical Trial Research Agreement. All departments offering services to facilitate the trial must have agreed to the internal budget and each Department Head must have signed a Declaration C form in the SSA.
    - The fees negotiated with the Clinical Trials Pharmacist at CHW must also be included in the CTRA submitted with the SSA.
2. **Medicines Australia Standard Indemnity Form**
    - This can be accessed at: http://medicinesaustralia.com.au/issues-information/clinical-trials/indemity-and-compensation-guidelines/
3. **Certificate of Insurance**
    - This is required to demonstrate that the appropriate insurance is in place to cover the Investigators and Hospital as set out in the Indemnity Agreement.
    - It must list an Australian entity as the insured and provide a minimum of $AU20million per occurrence.
4. **CTN / CTX Form**
    - A completed CTN or CTX form should be submitted with your Research Governance application for signing by the Director of Research. A copy of the signed form will be provided to you with your approval letter.
    - "The Sydney Children's Hospitals Network (Randwick and Westmead) incorporating The Royal Alexandra Hospital for Children" should be named as the Study Sponsor for investigator-driven trials (TGA ID Code: 17753). The Director of Research of SCHN will be responsible for signing this part of the CTN and this signature will be arranged by the Research Governance Office upon approval of the project by the HREC. The Chief Executive will sign if the Director of Research is conflicted.

If conducting a clinical trial which is commercially sponsored the CTRA, Medicines Australia Standard Indemnity Form and Certificate of Insurance will be provided by the sponsor.

If your trial is not industry sponsored discuss these requirements with the Research Governance Office prior to submission.

3.3.5 Research Governance Approval Process

- All clinical trials to be conducted at SCHN requires Governance approval in addition to Ethics approval.

- Following Ethics approval, the Research Governance Office will assess the SSA and any accompanying documentation, and determine whether it is appropriate for the research project to be conducted at any site under SCHN.
- The Research Governance Office will then recommend to the Director of Research or CE to approve the site the conduct of the research project. The Research Governance Office will then issue a Site Specific Approval Letter under the authorisation given by the Director of Research or CE.
- Investigators can only begin their clinical trial or research project once the Site Specific Approval Letter has been received and the TGA CTN or CTX acknowledgement (for trials involving drug or device) has been received.

4 Required Standards – Good Clinical Practice

4.1 What is Good Clinical Practice (GCP)?

Through the efforts of the International Conference on Harmonisation (ICH), a set of standard principles for the conduct of clinical trials were determined and set out in the World Medical Association's Declaration of Helsinki.[3]

These have been accepted by the TGA which has adopted the European Union version of the ICH Good Clinical Practice (GCP) guideline in Australia1 with respect to GCP and clinical trial conduct in general.

- GCP is a Code of ethical conduct and applies to everyone and all studies.
  The code:
  - Provides information on how trials should be conducted
  - Provides a template on which to create a paper trail and therefore guard against fraud
  - Protects all people involved in clinical trials

All clinical trials performed at SCHN or by staff of SCHN must be conducted according to Good Clinical Practice standards and it is a requirement that all staff working directly on clinical trials attend GCP training at least every two (2) years.

4.2 Investigator and Sponsor Responsibilities

4.2.1 Investigators

The following responsibilities are GCP, Ethics, Research Governance and TGA regulatory requirements:

- NEAF Preparation.
- Submission of NEAF and SSA to Ethics and Research Governance.
- Maintenance of Trial Master File (see Section 4.3.1 for more details).
- Ensuring adherence to HREC and Research Governance conditions of approval.

- Must provide medical care to trial participants that are necessary as a result of any adverse events experienced during or following the trial that is related to the trial.
- Documentation of accountability of the investigational product is maintained.
- Ensuring "Obtaining Informed Consent SOP" is followed.
- For further details please read section 4 of the Note for Guidance on Good Clinical Practice.[1]

4.2.2 Sponsors

The sponsor is an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

The role of sponsor in a clinical trial usually is determined by the entity who developed the study protocol and who has the resources to properly take on the sponsorship responsibilities. As such, a number of different entities may sponsor a clinical trial:

1. Commercial entity – such as a pharmaceutical company;
2. Collaborative group – e.g. an Oncology cooperative / collaborative group;
3. Hospital-sponsored trials – where the study has been developed by an employee/s of the hospital (known as an 'investigator-initiated' trial) the hospital may agree to take on those sponsorship responsibilities. For some of these trials, a pharmaceutical company will only provide the drug to the investigators for the study, but will not accept sponsorship of the study. In these cases, the hospital may agree to sponsor the study and take on those responsibilities.

From a TGA perspective, the sponsor of a clinical trial is that individual who endorses the CTN or CTX form. A sponsor must be an "Australian Entity" for the purposes of the CTN or CTX.

In such a situation, an international commercial entity may engage a local company, known as a Clinical Research Organisation (CRO), to run their trial in Australia and take on the sponsorship responsibilities.

The responsibilities of a trial sponsor with respect to GCP are extensive and detailed in section 5 of the Note for Guidance on GCP[1] and involve:

- Overall trial management including ensuring Quality Assurance and Quality Control systems are in place to ensure trials are conducted appropriately; data handling, record keeping, analysis and publication is conducted in compliance with GCP, the trial protocol and any TGA requirements.
- Provision of appropriate insurance and indemnity for the trial and trial-related staff, as well as measures for subject compensation for trial-related injury.
- Ensuring the confirmation of endorsement from the relevant HREC(s) and notification of the approval etc. to the TGA.
- Ensuring appropriate manufacture, packaging, labeling/coding and distribution to trial sites of all investigational medicinal products.
- Ongoing safety evaluation and AE/ADR reporting as described earlier in this document.

- Compliance with Monitoring/Audit/Inspection requirements.
- Notification of any premature termination of the trial in question.
- Completion of the Clinical Study Report.

4.3 Trial Documentation: Essential Documents

The essentials of trial documentation are detailed in section 5 of the Note for Guidance on GCP.[1]

These documents allow the assessment of a clinical trial as to whether it complies with the standards of GCP, in terms of the conduct of the trial and the quality of data generated. Thus they are an objective means of verifying GCP.[1]

All clinical trials conducted at SCHN or by employees of SCHN must be supported by the essential trial documentation that is required to adhere to good clinical practice standards

Assistance to establish the essential trial documentation can be sought from Clinical Research Centre.

4.3.1 Trial Master File

This should be established at the commencement of a trial at both the Chief Investigators/Institution's site and at the Sponsor's place of business. The trial master file contains all the regulatory documents from ethics and governance, including communication between all parties and must be maintained for the duration of the study.

The following lists include examples of documents that may be contained within the Trial Master File:

Before Trial Commencement

- All documents submitted to Ethics and Governance for Approval.
- Letters of Approval from Ethics and Governance
- Curriculum Vitae of investigator(s) and sub-investigators to be submitted with the Site Specific Application form.
- Certificates of Analyses and compliance with (GMP) for investigational products (if required).
- Decoding procedures for blinded trials.
- Master randomisation list.

During the Trial

- Investigator brochure updates.
- Dated approvals for revisions of protocol, informed consent, advertisement, ongoing trial review, patient information documents.
- Curriculum Vitae for new investigators.
- Monitoring visit reports.
- Signed informed consent forms.

- Notification to sponsor and HREC of serious AEs.
- Notification to TGA of serious and unexpected ADRs.
- Annual reports of study progress.
- Investigational products accountability documents.

After Trial Completion

- Investigational product accountability.
- Subject identification code list.
- Final close-out trial monitoring report.
- Clinical study report.

4.3.2 Clinical Trial Protocol and Protocol Amendment(s)

The protocol sets out all study procedures and dictates how the study will be run. It must be followed strictly throughout the trial. Any change must be submitted to the SCHN HREC or original Lead HREC and Research Governance Office as an Amendment for approval before the proposed changes can be implemented.

4.3.3 Participant Information and Informed Consent

The decision to participate in a clinical trial is voluntary and must be appropriately informed. Each participant that takes part in a clinical trial study must give written informed consent before beginning the trial. The Participant Information and Consent Form must be placed in the investigators file and a copy placed in the participant's medical record. A copy must also be given to the participant and this action must be recorded in the medical record

4.3.4 Case Report Form (CRF)

A Case Report Form (CRF) is required for each participant entered into a clinical trial. The CRF includes all information required for the study (e.g. test results, dosage times, AEs, concomitant medication etc.). The identity of the participant is confidential so only study numbers and/or initials will appear on the CRF. It is common now for Case Report Forms to be electronic.

4.3.5 Investigators Brochure

A clinical trial must have an up-to-date Investigator's Brochure (IB). A minimally sufficient Investigator's Brochure is outlined in item 7.2 of the Note for Guidance on GCP[1].

4.4 Clinical Trial Development and Management

4.4.1 Protocol development

Protocol development occurs prior to completing the NEAF or submission to Ethics. The protocol is generally provided for Industry sponsored trials whereas Investigators will be required to write a Protocol if funding has been obtained from elsewhere. A protocol template can be found on SCHN intranet. The protocol has to be submitted with the NEAF when applying for HREC approval.

4.4.2 Study Feasibility

Determine if you require the support / assistance of other departments to conduct your study. Please refer to the Policy: "Human Research (Clinical) Utilisation of Hospital Resources" for assistance in setting up trials or contact the Centre Manager for the Clinical Research Centre at either The Children's Hospital at Westmead or Sydney Children's Hospital.

4.4.3 Budget development

To determine the trial budget, the investigator is required to consider all of the services, consumables, staff time etc. required for the proposed protocol and obtain costs for each item. Full industry sponsored trials generally cover all clinical trials costs. For collaborative group and investigator initiated trials all costs that are not standard treatment in the routine care of the patient (e.g. pathology tests, x-rays, medicine dispensing) will need to be incorporated in the budget. These costs should also be taken into consideration when applying for research grants.

Investigator driven trials must be self-funded or paid from Departmental research or SPT funds. Industry sponsored studies must include all fees and charges in the budget. The investigator must determine whether the funding offered is sufficient to cover all costs before the Clinical Trials Agreement is finalised.

Pharmacy, Ethics and Governance fees may be negotiated for Investigator- driven studies depending on the complexity of the trial and the amount of external support, if any, provided. The Clinical Trials Pharmacist must be notified during budget development as pharmacy fees are directly negotiated with the sponsor of the trial Clinical Trials Pharmacist prior to finalising the budget and submitting the application to Ethics and Governance.

All considerations should be included in the budget of the ethics application and, for Industry sponsored trials, the Clinical Trial Research Agreement.

4.4.4 Quality Assurance (QA) Checks

Each study must have regular QA checks either by the Industry monitor or by internal QA activities. A copy of the documentation verifying that these checks have taken place is stored in the Investigators File.[1]

4.4.5 Trial Registration

All clinical trials should be registered prospectively (i.e. before the first patient is recruited) on The Australian New Zealand Clinical Trials Registry: http://www.anzctr.org.au/ or other international Clinical Trials. It is the sponsor's responsibility to register a trial.[11] For investigator-initiated studies, it is the Investigator's responsibility to register the study appropriately.

4.4.6 Safety Reporting

Requirements for safety reporting in clinical trials are detailed in the "The NHMRC Australian Health Ethics Committee (AHEC) Position statement: Monitoring and reporting of safety for clinical trials involving therapeutic products, May 2009" and the TGA's publication, "Access to Unapproved Therapeutic Goods – Clinical Trials in Australia"[6] and Note for guidance on clinical safety data management: definitions and standards for expedited reporting[7]

The Note for Guidance on GCP[1] describes the required reporting of such adverse reactions and events.

Please also refer to the SCHN policy: "Safety Monitoring and Reporting of Clinical trials" and the Adverse Event Report Forms available from the ACCT Centre.

4.4.7 Data Analysis

The analysis of data should be performed prior to breaking the treatment code whenever possible. In some instances (e.g. Multi-centre studies), this task is performed by the sponsoring drug company or by an independent organisation appointed by the drug company.

4.4.8 Study Report

A study report should be written either by the Sponsor, the CRO or by the investigator.

4.4.9 Publication / Dissemination

Every study should be published (even negative results).

4.4.10 Archiving

All studies must be archived at the completion of the study. Paediatric studies in NSW must be archived for fifteen (15) years or until the youngest participant turns twenty-five (25) whichever is longest. Please contact the Clinical Research Centre to discuss available options at the completion of your study. Pharmacy has separate archiving for all pharmacy related documentation - dispensing summaries, original prescriptions, original or copies of the subject's enrolment and accountability logs.

5 Pharmacy Clinical Trials Service

The primary aim of the Pharmacy Clinical Trials Service is to optimise patient outcomes by working to achieve the best possible quality use of investigational medicines. This is achieved by following The Society of Hospital Pharmacy of Australia (SHPA) Standards of Practice for Pharmacy Investigational Drugs Services[8].

The Director of Pharmacy is responsible for the storage of all restricted substances, including investigational drugs at the hospital other than those that have been supplied to a ward storage facility.[9]

All medicines dispensed as an investigational product (IP) during the conduct of a clinical trial must be treated as prescription-only medicines and only supplied prescription, by a medical officer, who is either a Principal investigator, Associate investigator or authorized by the Principal Investigator.

An independent Pharmacy Clinical Trials Service:

- avoids conflicts of interests
- ensures prescriptions and dispensing's are appropriately documented in the patient medication history
- maintains clinical governance
- for multi-centre trials – ensures consistency in investigational drug management

- supports and promotes the safe and ethical use of investigational drugs;
- ensures the principles of pharmaceutical care are applied to the evaluation of new drugs;
- ensures pharmacy aspects of investigational products use comply with relevant Acts, Standards and Professional Codes of Practice;
- considers the welfare of study participants and the protection of their rights and confidentiality;
- supports and promotes medical research[8]

The Pharmacy Clinical Trials Service generally provides the following services:

- stock management, dispensing and control of all investigational products
- appropriate storage and environmental monitoring
- destruction of IPs, if permitted by the protocol
- emergency 24 hour access to the service
- assistance with adherence to study protocol
- counselling of participants and monitoring compliance
- provision of information to participants and their carers, medical and nursing staff, other pharmacists
- review of protocols
- organisation of a review of the study protocol by the hospital Drug and Therapeutics Committee, as required
- provision of advice on study design and/or protocol development
- development/allocation of randomisation codes (eg for blinded studies)
- preparation of placebos and special dosage forms
- aseptic reconstitution when required
- adverse drug reaction reporting
- literature searches
- collection and analysis of data
- education of pharmacists, pharmacy students and other healthcare professionals
- procedures associated with trial completion
- archiving of all pharmacy records for a minimum of 23 years for paediatric studies
- ensures adherence to the Society of Hospital Pharmacists of Australia standards and guidelines and other regulatory guidelines

For further information:

- On access to the Clinical Drug Trials Service and fees involved refer to the Policy "Human Research (Clinical) Utilisation of Hospital Resources"

- The current NSW Teaching Hospitals Pharmacy Departments guidelines are applicable for all sponsored trials involving investigational drugs and more information can be obtained from:
    - At Children's Hospital at Westmead: The Clinical Trials Pharmacist at (for the Children's Hospital at Westmead trials)
    - At Sydney Children's Hospital: the Centre Manager (for Sydney Children's Hospital trials).

6 References

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4. National Statement on Ethical Conduct in Human Research http://www.nhmrc.gov.au/publications/hrecbook/02_ethics/05.htm (accessed 27/10/2014)
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6. Access to unapproved therapeutic goods – Clinical Trials in Australia http://www.tga.gov.au/pdf/clinical-trials-guidelines.pdf (accessed 27/10/2014)
7. Note for guidance on clinical safety data management: definitions and standards for expedited reporting: http://www.tga.gov.au/pdf/euguide/ich37795.pdf (accessed 27/10/2014)
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