RWH CLINICAL TRIALS INSTRUCTIONS

Application Fees to conduct a Clinical Trial

1. Fees payable to the Therapeutic Goods Administration (TGA) if applicable

CTX & CTN Clinical Trials--- As required by TGA.

2. Fees payable to The Royal Women's Hospital

Clinical Trials are often initiated by a commercial company or other organization, who become the "Commercial Sponsor" of the trial. If no organization external to the hospital is involved, the trial is considered to be unsponsored. In reporting to the TGA, "The Royal Women's Hospital" is named as the "Sponsor".

For commercially sponsored clinical trials, an application fee is levied. This fee is to enable expert external review of the trial protocol, and is a contribution toward the large administrative requirements of Clinical trials.

Payment to the Hospital must accompany the application.

Commercially Sponsored CTX Trials --- **$4,400** (GST included)

Commercially Sponsored CTN Trials, Phase II --- **$4,400** (GST included***)***

Commercially Sponsored CTN Trials, Phase III and IV --- **$3,300** (GST included)

All legal and regulatory costs for Clinical Trials are at the expense of the sponsor or investigator.

Regulations for Clinical Trials

The Therapeutic Goods Administration (TGA) is the Australian Regulatory body for all clinical trials involving drugs, vaccines or therapeutic devices. The TGA has two schemes for regulation of clinical trials.

Clinical Trial Notification (CTN) Scheme - The data is reviewed only by the technical reviewers and Human Research Ethics Committee of the Institution. The TGA does not review data relating to the trial before permitting it to proceed. The sponsor or investigator notifies the TGA that a clinical trial is to be conducted after the HREC has given approval.

Clinical Trial Exemption (CTX) Scheme - The TGA evaluates data to assess safety issues and decides whether the proposed usage guidelines for the product are acceptable.

The TGA reviews:

- a pharmaceutical chemistry checklist or full pharmaceutical data for biological materials
- pre-clinical data
- clinical safety data
- summary documents provided to the ethics committee, including the usage guidelines

The HREC then considers the proposed trial protocol after reviewing the summary information provided by the sponsor and additional comments from the TGA.

Notification to the TGA under the CTN scheme or application to the TGA under the CTX scheme is required for clinical investigations involving:

a) any drug product not entered in the Australian Register of Therapeutic Goods (ARTG), including any new formulation of an existing drug product or any new route of administration; and

b) any use of a marketed drug product beyond the conditions of its marketing approval, including new indications extending the use of a drug or drug product to new patient groups (for example children, pregnant women or the elderly) and extending the doses or duration of treatments outside the approved range.

Under both schemes, the study must be approved by the HREC and the Hospital's insurers, Victorian Managed Insurance Authority (VMIA) where applicable.

Researchers are encouraged to familiarize themselves with the VMIA Insurance Guidelines for Clinical Trials for Victorian Public Hospitals at http://www.vmia.vic.gov.au/Risk-Management/Clinical-trials.aspx

Drug Trial Phases

Phase I trials - The first administration of the drug to humans.

The drug is administered to small numbers of volunteers, usually healthy, but sometimes patients, for the purpose of determining pharmacological activity, tolerance absorption, distribution, metabolism and excretion. These studies should be carried out in a closely supervised setting in conjunction with a laboratory appropriately equipped for the specialized monitoring and the high degree of surveillance required. Data from these studies should identify the preferred routes of administration for subsequent trials.

Phase I studies will only be considered by The Royal Women's Hospital in exceptional circumstances.

Phase II trials - The first trials of the drug in patients suffering from the disorder for which the drug is intended.

The purpose of these trials is to determine efficacy and safety in a small number of closely supervised patients. The trials are usually conducted by investigators regarded as specialists in the particular disorder and its treatment. Several doses of the drug are often used to establish the therapeutic range and the maximum tolerated dose. These principles also generally apply to vaccine evaluation.

The phase I and phase II protocols must have been reviewed by one of the accepted regulatory authorities. At least phase I trials must have been completed and the results fully documented and available for review by the Committee. Data must show that the potential benefits of the trial outweigh possible hazards. The studies will be presented initially to a phase II subcommittee to determine if the application is considered suitable before a thorough review is conducted. All phase II trial applications must be submitted to the Hospital solicitors and insurers for consideration, at the trial sponsor's expense.

Phase III - Extended clinical trials.

These trials involve numerous patients and are undertaken by experienced clinical Investigators when data from Phase II studies indicate that the drug has a potential benefit, which outweighs possible hazards.

To conduct Phase III trials under the CTN scheme, the requirements of the Hospitals Public Liability/Malpractice Policy are:

a) The drug must have been approved for marketing or clinical trial by one of the accepted regulatory authorities, for the use, dose, duration of treatment and broad patient groups proposed for the clinical trial.

b) The clinical trial must be in Phase III of the generally accepted clinical trial classification, that is:

   i) data from Phase II studies indicate that the potential benefits of the trial outweigh possible hazards, and trials must have been completed, the results fully documented and available for review by the Committee.

   ii) the purpose of these trials is to ascertain whether the drug confers clinical benefit in the disease states for which effectiveness is to be claimed, with an acceptable incidence and nature of adverse events.

Phase IV - Post marketing trials.

These trials involve the use of a drug with an approved indication, formulation and route of administration. They are designed to extend the information developed in pre-marketing trials.

Grandfather Drugs

These are drugs which came into clinical use before the institution of Government regulations. Current regulations require demonstration of a new drug's pharmacological properties and appropriate toxicological studies in animals prior to administration to humans, together with extensive clinical studies to evaluate the drug's efficacy and relative safety before approval for marketing.

Post-study Availability of the Drug/Device

Please provide the details of any drug company incentives in regard to cheaper drug pre-registration or Pharmaceutical Benefits Scheme (PBS) listing. It is more favourable if the drug will be free or cheaper until PBS listing. For post-study use of medication, prescribers must provide the Drug Usage Committee evidence of the benefit and the possible harm of the medication before continuing the use of medication. Prescribers must also justify the use of the new medication and its advantages over existing therapies.

Definition of Accepted Regulatory Authorities

Any previous review of the trial by one of the accepted regulatory authorities must be declared.

- Australia - Therapeutic Goods Administration (TGA)
- United States of America - Food and Drug Administration (FDA)
- United Kingdom - Medicines Control Authority (MCA)
- Canada - Canadian Drug Administration (DCA)

- Sweden - Swedish Medicines Agency

What Phase drug trials can be conducted by The Royal Women's Hospital?

The Royal Women's Hospital will consider Phase II, III and IV trials under the CTN Scheme. All Unsponsored trials need to be approved by the Hospital's insurers. Phase I trials should be submitted via the CTX scheme. **All legal and regulatory costs for Clinical Trials are at the expense of the sponsor or investigator.**

The Signed cooperation of the **Department of Pharmacy** is required for all Drug Trials.

Definition of a Therapeutic Device

"An instrument, apparatus, appliance, material or other article (whether for use alone or in combination), together with any accessories or software required for its proper functioning, which does not achieve its principle intended action by pharmacological, chemical, immunological or metabolic means though it may be assisted in its function by such means. It is a medical device that has not been used in humans or not been registered or listed on the Australian Register of Therapeutic Goods."

Therapeutic Device Trials

All trials involving therapeutic devices need to be submitted to the Hospital Insurers for consideration of insurance coverage under the Public Liability/Malpractice Policy.

Additional information that must be included in the Participant Information and Consent Form

In addition to the standard requirements for the Participant Information and Consent Form, the following information should be included if relevant

- A statement regarding current registration status in Australia
- An explanation that a placebo (inactive substance) is involved
- The explanation of adverse effects from the drug or the procedure proposed should include a comparison of the other drugs or procedures currently used for the same purpose.

Indemnity

Applications for trials involving an external sponsor must be accompanied by a copy of the standard Medicines Australia Form of Indemnity for Clinical Trials, signed by a representative of the Sponsor. The pro forma form is available in the VMIA Insurance Guidelines at

http://www.vmia.vic.gov.au/Risk-Management/Clinical-trials.aspx

Two (2) Original copies are normally required. One (1) is retained on file with the Principal Investigator records and the other is returned to the Sponsor.

Clinical Trial Agreements

It is a condition of the Hospitals Public Liability/Malpractice Insurance that there be a written Clinical Trial Agreement for all sponsored drug or device trials.

The agreement needs to be between the Sponsor, The Royal Women's Hospital and the Investigator. Ensure correct addresses are provided and provision is made for each party to sign the agreement.

This agreement must delineate clearly the responsibilities of the Sponsor, Investigator and the Institution. including responsibilities for compensation/treatment in the case of injury or death, and for any insurance indemnity to cover the liability of each of the parties involved.

Two (2) Original copies are normally required. One (1) is retained on file with the Principal Investigator records and the other is returned to the Sponsor.

The Clinical Trial Agreement must include the following information

The Sponsor must:

- Clearly identify a person ("the Monitor") to be its principal link with the Investigator.
- Provide the Investigator and HREC with accurate, current information about the drug product prior to the agreement being made.
- Monitor the application of the drug product in other places (elsewhere in or outside Victoria or in other countries) and advise the Investigator, HREC and TGA of the cessation elsewhere of any relevant trial or the withdrawal of the drug/device from any other market for safety reasons.
- Provide a signed standard form of indemnity as set out in the attached Indemnity. Any different form of wording requires specific approval by The Royal Women's Hospital lawyers at the Sponsor's expense.

The investigator must:

- Report to the Sponsor (within 24 hours) and the HREC (within 72 hours) any significant, adverse drug effect experience during the trial by any Participant (after becoming aware of same).
- Maintain all records relating to the study for a period of fifteen (15) years in the case of adults, and twenty-three (23) years in the case of children.

*Register your clinical trial with the Australian New Zealand Clinical Trials Registry

From 1 July 2005, the International Committee of Medical Journal Editors (ICMJE) will only consider publishing clinical trials that have been registered with The Australian Clinical Trials Registry before the enrolment of the first participant. For ongoing trials, they should be registered before 13 September 2005.

The Australian New Zealand Clinical Trials Registry is a national on-line registry of all types of clinical trials being undertaken in Australia. It has been established by the Federal Government and is situated at the NHMRC Clinical Trials Centre, University of Sydney.

Researchers who wish to publish their clinical trials should therefore register their trials with the Registry. The Registry will include information about:

- clinical trials into pharmaceuticals, surgical procedures, preventive measures, lifestyle, devices, rehabilitation strategies and complementary therapies; and

- all clinical trials involving Australian researchers and participants and covering all areas of health.

Background and relevant web site at: http://www.anzctr.org.au/