Health
Sydney
Local Health District

CLINICAL TRIALS

WHAT IS A CLINICAL TRIAL?

A *clinical trial* is a research study designed to test the safety and effectiveness of a treatment.
Most often, this is a drug treatment, but any form of treatment can be studied in this way, including surgical treatment, alternative therapies and new techniques such as gene therapy. Clinical trials of drugs usually involve the testing of a newly developed drug, but they can also be done to study new uses for an existing drug, new doses, or new treatment combinations, or to compare existing standard treatments.

HOW IS A NEW DRUG TESTED?

Before human trials begin, a new drug usually undergoes extensive testing in animals. These *pre-clinical* studies are designed to examine the tissue effects of the drug, the way it is processed in the body, and its potential to produce toxicity or birth defects. It must generally also be certified as having been produced according to *Good Manufacturing Practice* principles and checked for purity and stability.

HOW ARE CLINICAL TRIALS OF NEW DRUGS CONDUCTED?

Phase I trials involve small numbers of individuals.
In these studies, researchers determine the best method of administration (eg, by mouth, IV drip, injection), how often the drug needs to be given, and a safe range of doses. Participants are also monitored very closely to identify any potentially harmful side effects.
Phase II trials involve a larger group of patients to see what treatment effects the drug has, and to further evaluate safety. If the drug appears to be safe, and if its effects look promising, it may progress to the next phase.
Phase III trials are much larger studies, usually involving many hundreds or thousands of patients divided into different treatment groups. The aim is to compare the treatment effectiveness and side effects of the new drug

with that of standard treatments (where they exist). If the results of these phased clinical trials show that the drug is safe and effective, it may be **registered** (licensed for marketing) by the Therapeutic Goods Administration (TGA).

Phase IV studies are conducted after a drug has been released onto the market. They mainly involve comparison with medicines already recognized as having a place in the treatment of the disease or with a range of other therapies.

Post-marketing surveillance

After release of a new drug onto the market, pharmaceutical companies, doctors and the TGA remain on the lookout for rare but important side effects not picked up in earlier clinical trials. Identification of serious side effects can lead to the drug being withdrawn from the market.

HOW IS TREATMENT EFFECTIVENESS DETERMINED?

There are many pitfalls in trying to work out whether a new treatment is truly effective. Study results can be influenced by unconscious treatment choices, the expectations of researchers and patients, and a range of other factors unrelated to the treatment. *Phase III* clinical trials use a number of methods to ensure that the results are reliable. Treatment comparison groups usually involve a *test group* (given the new treatment) and a *control group* (given the standard treatment). If there is no standard treatment of proven value, or if it has worrying side effects, a *placebo*—a look-alike or 'dummy' pill that contains no active drug—may be used in the control group. Allocation to one or other treatment group is generally determined by a computerised lottery method known as *randomisation.* Ideally, neither researchers nor participants should know which treatment a particular person is having. Studies of this kind are referred to as *double blind* trials. Safety comes first, though—if a participant develops an unexpected or serious problem while on a trial, the treatment code can be broken and appropriate action taken.

WHO CONDUCTS CLINICAL TRIALS?

Conducting a clinical trial is a team effort. The team is usually led by a senior clinical researcher—the *principal investigator*—and may include specialist doctors, general practitioners, nurses, counsellors, pharmacists, laboratory scientists, and many other behind-the-scenes support staff. Because of the large number of patients needed for *Phase III* clinical trials, these studies are often carried out in many research centres around the world and are known as *international multicentre* trials. Principal investigators from the major centres often form a *steering group* to make sure there is proper communication and coordination between participating centres.

WHO PROVIDES FUNDING FOR CLINICAL TRIALS?

All clinical trials must have a *sponsor*. This can be an individual, a company, an institution, or an organisation that takes responsibility for the initiation, management, and/or financing of a trial. About 80% of clinical trials conducted at SLHD are commercially sponsored and funded, in most cases by a pharmaceutical company. The remainder are initiated by a researcher or group of researchers, and are sponsored by the Local Health District. Funding can come from grant-giving bodies such as the National Health & Medical Research Council or one of the many non-government fund-raising organisations, or researchers and the hospital may absorb the costs of running a trial. It is not considered ethical for clinical trial costs to be charged to patients, health insurance companies, or Medicare. Sometimes, however, patients may be billed for those aspects of their treatment that would otherwise be part of their routine care, such as medical consultations, blood tests, X-rays or scans. Trial participants may be reimbursed for out–of–pocket expenses associated with the trial and, in some studies, you may receive a small amount for the time and inconvenience involved.

WHO CAN PARTICIPATE IN A CLINICAL TRIAL?

Each clinical trial has guidelines drawn up that specify which patients are suitable *(inclusion criteria)* or unsuitable *(exclusion criteria)* for the particular study. These criteria are based on factors such as age, type of disease, medical history and current medical condition. The purpose is to make sure that the study is suitable for the patients who are enrolled in it and that the risks are minimised.

WHAT IS THE ROLE OF THE ETHICS COMMITTEE?

All clinical trials must be reviewed and approved by an ethics committee before they begin. The ethics committee provides ongoing oversight and protection of the interests of the participants. The membership, responsibilities and operating procedures of ethics committees are governed by a set of guidelines called the *National Statement on Ethical Conduct in Human Research* (2007, updated March 2014).

There are two ethics committees within the SLHD - one based at Royal Prince Alfred Hospital and one at Concord Repatriation General Hospital. They are widely representative committees with up to half the members being non-medical, several of whom are not associated with the hospital in any other respect.

The committees have reporting responsibilities to:

- *The Board of the Sydney Local Health District*
- *The NSW Department of Health*
- *The Australian Health Ethics Committee (of NHMRC)*
- *The Therapeutic Goods Administration (TGA)*

When a new clinical trial is submitted for ethics approval, an expert sub-committee first examines the scientific, technical and safety aspects of the trial, and may request modifications to the research plan if it has any concerns.

Once the expert sub-committee is satisfied with the study plan, all other aspects of the trial are scrutinised by the ethics committee, including:

- *The risks and benefits of the trial*
- *The process of recruiting and enrolling patients*
  The plain language information statement which is given to those considering joining the trial
- *The consent procedures*
- *Privacy and confidentiality issues*
- *Financial arrangements and potential conflicts of interest*
- *Insurance and compensation arrangements*

- *Safety monitoring arrangements*

The ethics committee may require additional modifications, and will only give approval for recruitment to begin when it is satisfied with all aspects of the trial.

WHAT ARE THE RESPONSIBILITIES OF SPONSORS AND RESEARCHERS?

Clinical trial sponsors and researchers have a responsibility to ensure that:

- *The resources for running the trial are in place, including adequate funding, experienced professional and support staff, and suitable facilities*
- *Ethical approval has been obtained*
- *Relevant regulatory guidelines are followed*
- *High research standards are maintained*
- *Careful safety monitoring is undertaken*
- *Any unexpected or serious adverse events are dealt with and reported promptly*
- *There are appropriate provisions for compensation if anyone is seriously injured as a result of their participation in a clinical trial*

Large international trials often have an independent *Data & Safety Monitoring Board* which conducts regular reviews and can recommend that a trial be stopped if unacceptable risks are identified. In addition, if there are local concerns the TGA can stop a trial, or can suspend it and require that changes be made to protect the participants before it can continue.

WHAT ARE THE RISKS AND BENEFITS OF BEING IN A TRIAL?

The main risks of clinical trials are:

- *The treatment you receive may turn out to be ineffective*
- *Unforeseen side-effects or adverse reactions to the trial treatment*
- *Pain or discomfort associated with tests required by the trial*
- *Time and inconvenience associated with frequent trips to clinics, hospital stays, complex treatments, tests, etc.*

Direct benefits may include:

- *Gaining access to new treatments that are not available to the general public*
- *Obtaining expert medical care at a leading research centre. (Even being in the 'control' group of a trial can lead to better health outcomes.)*

Other benefits are less tangible:

- *A sense of empowerment from becoming well informed about your illness, and playing an active part in your own health care*
- *Helping others in the future by contributing to a global research effort*

WHAT ARE MY RESPONSIBILITIES AS A TRIAL PARTICIPANT?

If you decide to participate in a clinical trial, you will be expected to:

- *Accurately report your medical history*
  Let your doctor know if you're taking anything else (including herbal medications, vitamin supplements, oral contraceptives, illicit drugs etc.)
- *Adhere to all safety and monitoring requirements*
- *Attend all scheduled appointments*
- *Take trial medications exactly as prescribed*

- *Keep all trial medications out of the reach of children*
  Inform your study doctor promptly if you develop any unexpected symptoms or new problems

WHAT ARE MY RIGHTS AS A TRIAL PARTICIPANT?

Participation in a clinical trial is entirely voluntary.

You cannot be enrolled without giving your written *informed consent*. Researchers are under an obligation to answer all your questions honestly; to make your welfare their primary concern; not to apply pressure or coercion to get you to join or stay in a trial; and to protect your privacy and keep all personal information about you confidential. If you decide to participate, and later change your mind, you can withdraw at any time. Whatever your decision, it will not affect your relationship with your health care team or with the hospital. You will be given a copy of the plain language information about the trial to keep. This has contact details for the researchers as well as the ethics committee.

If there are any irregularities, or you have concerns or complaints about a trial you're involved with, you can contact the ethics committee. Your concerns will be dealt with speedily and confidentially.