

Clinical Trials Process

The purpose of a clinical trial is a test to see how a drug performs in humans, and to develop, test and make available information to provide a basis for **Evidence-Based Medicine**. Evidence-based medicine is the principle behind the way doctors make choices between different treatments as they become available.

Evidence on the effectiveness of drug treatments is based largely on clinical trials. Before drugs can be tested on humans, there is a whole battery of tests conducted in the laboratory and on animals to assess their safety before the drug is given to humans.

A clinical trial is more extensive and thorough than first imagined. The scope of a trial can be vast, not only studying the drug itself, but examining diagnostic procedures; lifestyle behaviours that can increase disease transmission, and how a patient's quality of life can be improved while living with an illness such as chronic hepatitis B and C.

To delve into the clinical trials process further, we have been talking to Dr Hugh Harley, Head of Clinical Hepatology, and Megan Phelps, Clinical Research Co-ordinator of the Viral Hepatitis Centre at Royal Adelaide Hospital who have given us the following information...

What is a clinical trial?

A clinical trial can take many forms. A *prevention trial* examines a treatment, procedure or lifestyle change to see if a medical condition can be prevented; a *screening trial* may be embarked upon to find the best way to detect a disease, and a *diagnostic trial* can be done to find better tests or procedures for diagnosing a disease or condition. Not only this, but new treatments or drug combinations and their effects may be subject to *treatment trials*; *quality of life trials* explore ways to improve comfort and the quality of life for individuals with a chronic illness, and *compassionate use trials* aim to provide experimental therapies prior to final drug approval by authorities to patients whose options with other remedies have been unsuccessful. *Compassionate access* on the other hand, is not classed as a clinical trial, but an undertaking from a pharmaceutical company to make their drug available to patients at no charge. Having said this, compassionate access will still seek answers to valid questions. For example, in enabling a larger number of patients to be treated with the drug, an assessment of safety and toxicity in a larger number of treated patients will be possible; more than may have been treated in initial phase III studies.

Hepatitis B and C clinical trials, from Phase II to IV, are run as treatment trials; a study of a new drug on human volunteers that follows a formal study plan or protocol, which states what will be done, when it will be done, and why. The aim of a clinical trial is to determine whether a drug is both safe and effective as a treatment for a particular disease, and can also help determine better ways to use pre-existing drugs.

The development of new drugs, from idea to marketing, is very time consuming and costly. The pharmaceutical industry estimates that out of every 10,000 ideas that begin in the lab, only 10 will ever reach the stage where they are tested on humans. Out of that 10, only one may reach the market. The process typically takes 10 to 13 years from initial work in the lab until a product is launched on the market. A drug on average will cost \$US800million from discovery to approval.

What are the design features of a clinical trial?

Clinical trials take the form of either pre-clinical, or Phase 1 through to Phase IV trials. Phase 1 clinical trials are generally targeted at healthy volunteers, as opposed to people with the condition the drug is aimed at who receive the trial drug in varying doses to assess safety and tolerability.

Most Phase II, III and IV clinical trials are run as active comparator (active control) studies, and will target the specific disease population. This means that the study compares the new study drug with a treatment that has known effects on a group of people with the disease.

A person who participates in a clinical trial may be assigned to a placebo group (see below for an explanation of a placebo), yet assigning a person to a placebo group creates an ethical problem when it means they will not receive the best available treatment, and therefore, if there is a standard of care available for the treating condition this must be used rather than a placebo. The standard of care is a current treatment option that is effective and already approved. If a standard of care does not exist, a placebo will be given and is known as a comparator study.

What is a placebo?

A placebo is a tablet, capsule or injection that looks like the trial drug, but contains no active ingredient; a placebo may be nothing more than a sugar pill.

Placebos are used in research trials to objectively test the efficacy of a new treatment where, usually, one group of people take the drug while another group (the control group) take the placebo.

Can you explain the placebo effect?

Results from both groups, both the control group taking the placebo and the group taking the new drug being trialled, should indicate the effectiveness of the new treatment. However, people sometimes get better when they are taking a placebo. This phenomenon is known as 'the placebo effect' and will affect about 1 in 3 people taking placebos.

The placebo effect is triggered by the person's expectation of feeling better. The theory behind such a phenomenon being that the belief in treatment may be enough to change the course of a person's physical illness.

Numerous factors exist that are believed to influence the placebo effect, including that the disease will often resolve on its own or a person may fall into remission. An improved diet, increased exercise, or rest may be adopted, and therefore the cause of improved health.

In addition, a placebo can often alter a person's perception; a person may feel better because they expect to feel better on treatment, and as a result, a reduction in anxiety may follow as stress releases adrenaline. If a patient believes they feel better, they are less stressed, produce less adrenaline, and are therefore left feeling less anxious and this reduces some of the side effects of their illness.

What might also occur with the taking of a placebo is the release of the brain's chemicals; placebos may trigger the release of the body's own natural painkillers, the brain chemicals known as endorphins.

Can you elaborate on the phases of a clinical trial described earlier, and what each phase involves?

Before pharmaceutical companies start clinical trials investigating a new drug, they have to determine the safety of the drug for administration in humans, so they conduct extensive pre-clinical studies.

Pre-clinical studies involve in vitro (test tube) and in vivo (animal) experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic information (the process by which a drug is absorbed, distributed, and eliminated by the body). Such tests assist pharmaceutical companies to decide whether a drug meets the standards for development as an investigational new drug.

Clinical trials involving new drugs are conducted in humans in four phases. Each phase has a different purpose and helps researchers answer different questions. The drug-development process normally proceeds through all four phases. If the drug successfully passes through Phases I, II, and III, it will usually be approved by the national regulatory authority; in Australia this is the Therapeutic Goods Administration (TGA) for use in the general population. Phase IV trials are 'post-approval' or 'post marketing' studies.

Phase I clinical trials

Phase I trials are the first stage of testing in human subjects. Normally, a relatively small number of healthy participants (20-50) will be selected, and this phase includes trials designed to assess the safety and tolerability of the new drug. In addition, they are conducted in an in-patient clinic where participants are closely monitored for any side effects, and the process by which a drug is absorbed, distributed, and eliminated by the body is tested.

Phase I trials include dose-ranging studies, also called dose escalation, so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing.

Furthermore, Phase I trials most often include healthy volunteers, however, there are some circumstances when real patients are used. Hepatitis B and C trials are one example where the viral activity is measured to test the efficacy of the new drug, therefore patients with hepatitis B and C need to be involved. Commonly, volunteers are paid an 'inconvenience fee' for their time spent in the volunteer centre in this phase of trials.

Phase II clinical trials

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed to treat larger groups (20-300 people) affected by the target disease. They are designed to provide the first evidence that the treatment is effective in patients with the target disease, and provide evidence that the treatment is safe in patients, as well as healthy people.

It is usually during Phase II trials that a drug is discovered not to work as planned, or to have toxic effects in longer term use.

Phase III clinical trials

Phase III trials involve a larger number of participants from a broad demographic of people with the disease (300–3,000 or more, depending upon the disease/medical condition studied). They consolidate and confirm safety, dosing, efficacy, side effects and cost-effectiveness across many ethnic backgrounds. At least two successful Phase III trials are required before approval by the appropriate regulatory agencies such as the TGA (Australia), FDA (USA) or EMEA (European Union) is given for the drug to be marketed.

Phase IV clinical trials

Phase IV trials take place after a drug has received regulatory approval based on the evidence gathered from Phases I to III trials.

Phase IV studies may examine dose variations in particular populations, for instance in overweight or underweight people, or people in various ethnic groups, and other populations such as children or the elderly. They may also examine the long term safety and cost-effectiveness of the drug, include a comparison with other agents and monitor drug interactions. They may also aim to gauge a better definition of toxicities, or examine new indications for treatment.

Can you please explain the differences between randomisation, blind trials and double blind trials?

Randomisation sees that each person participating in the study is assigned by chance to receive either the study treatment, or control group placebo or standard of care.

Blind trials are when the subjects involved in the study do not know which study treatment they are receiving. One step further are *double-blind trials* in which both the subject and the investigator do not know which treatment is being given to any person involved.

This 'blinding' is to prevent biases. It is thought that if a study nurse or doctor knew which patient was getting the study treatment and which patient was getting the placebo, he/she might be tempted to give the (presumably helpful) study drug to a patient who could more easily benefit from it. Alternatively, a study nurse or doctor might give extra care to only the patients who receive the placebos to compensate for their ineffectiveness.

Likewise, if a patient knew they were receiving a placebo rather than the trial drug, they might discontinue with the trial, influencing the final outcome in a negative manner.

Can you explain what placebo-controlled, multi-centre trials and open trials are?

An *open trial* is the opposite of a *double-blind trial* as both patients and investigators know which product each patient is receiving.

A *multi-centre trial* is a clinical trial conducted at more than one site by more than one investigator according to a single protocol, all abiding by the same guidelines.

Placebo-controlled trials use a placebo (dummy treatment), which allows the researchers to isolate the effect of the study treatment.

How important are sample sizes? What makes a clinical trial result a statistically significant result?

Any study needs to be designed to ensure that the number of patients included is sufficient to ensure that the results of the trial are meaningful or 'true'. There are statistical ways of calculating these numbers depending on the magnitude of the benefit that one predicts the study will demonstrate; smaller numbers will not give meaningful results.

The term 'statistically significant result', means that the result tells us something about the degree to which the result is 'true' in the sense of being representative of the population.

For a clinical trial to go ahead, the informed consent of the participants must be gathered. What does the informed consent of participants involve?

Informed consent is the process in which a person learns the key facts about a clinical trial, then agrees to voluntarily take part, or decides against participating. This process includes the patient receiving a specific Patient Information Document that describes the benefits and risks of participation in the clinical trial and signing the Informed Consent Form.

It is a requirement that informed consent be obtained and fully understood by a person before entering a clinical trial. The information included will outline the length and purpose of the trial, the medical procedures that will be undertaken, and the patient's responsibilities, such as the drugs to be taken. There are also questionnaires to be completed, and the benefits and risks to the patient and any costs involved explained. Alternative treatment options must also be made known to the patient, such as what treatments are available should the patient not be on the trial, and the patient's rights should be clearly stated.

A patient's rights include being told in no uncertain terms that their participation is voluntary and that they can withdraw from the trial at any time without jeopardising future care at the same institution at which the trial is being run. In addition, a patient has the right to be kept informed of developments in the trial.

After the patient has been informed of all the relevant details of the trial, the patient will be asked to sign the *Informed Consent Form*. This form must be personally signed and dated by both the participant and their investigator, and a copy given to the patient.

What guidelines do clinical trials have to adhere to?

Clinical trials are conducted under strict regulations and protocols determined by a governing body such as the Therapeutic Goods Administration (TGA) in Australia, or the US Food and Drug Administration (FDA).

In addition, clinical trials must be conducted in accordance with ethical guidelines.

The International Conference on Harmonization (ICH) Good Clinical Practice Guidelines, were adopted in 1996 as a universally accepted set of standards by which all clinical trials have to be performed in order for a drug to be accepted for marketing. Clinical trial protocols follow ICH guidelines aimed at 'ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost-effective manner'. These activities are pursued in the interest of the consumer and public health to prevent unnecessary duplication of clinical trials in humans, and to minimise the use of animal testing "without compromising the regulatory obligations of safety and effectiveness".¹

Who organises the trials, and who approves them? What are the roles of research institutes, drug companies and clinicians? Furthermore, what is the role of Human Research Ethics Committees?

Some treatment trials are initiated independently by clinical researchers, but most treatment clinical trials are sponsored by the pharmaceutical company developing the new drug/treatment. It is the sponsor's role to design and pay for the clinical trial.

Clinical trials of new drugs are often administered by a Contract Research Organisation (CRO) hired by the sponsoring company (the sponsor provides the drug and medical oversight) contracted to perform all the administrative work on a clinical trial. It recruits participating researchers, trains them, provides them with supplies, co-ordinates study administration and data collection, sets up meetings, monitors the sites for compliance with the clinical protocol, and ensures that the sponsor receives 'clean' data from every site.

A Principal Investigator is the individual responsible for the conduct of a clinical trial at the trial site and ensures that it complies with Good Clinical Practice Guidelines. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal or Lead Investigator. In this instance, they may delegate tasks to other team members.

The clinical co-ordinator is the key person in the Research Staff; he/she works closely with the Investigator and the participant to ensure that the study follows the protocol and that treatments and procedures are administered correctly, and that administrative paperwork is completed accurately.

The (Human) Research Ethics Committee (REC) is a group of scientists, doctors, clergy and lay people who review research protocols involving humans or animals based on Good Clinical Practice (GCP). RECs are designed to protect the patients who take part in research and as such, clinical trials must be approved by RECs before being implemented. They check to see that the study is well designed, does not place the participant under undue risk, and includes safeguards for participants.

What is Good Clinical Practice in regards to clinical trials?

Good Clinical Practice is a standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the

¹ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidelines for Good Clinical Practice, 1 May, 1996

data and reportable results are credible and accurate and that the rights, integrity and confidentiality of the participants are protected.

How does someone join a clinical trial?

The Australian New Zealand Clinical Trials Registry (ANZCTR) is an online register of clinical trials being undertaken in Australia and New Zealand. It covers all clinical trials involving Australian or New Zealand researchers or participants.

Trials may also be advertised in either the local papers, national papers or on radio, and flyers are often put up in GPs' and specialists' rooms and hospitals - many patients will enter a clinical trial for hepatitis B or C through the patient's treating hospital if the hospital is involved in clinical trials.

Hepatitis Australia, and the state and territory based hepatitis organisations are also often aware of clinical trials and locally participating hospitals.

Why should someone join a clinical trial? What are the benefits?

Clinical trials help assess if new treatments are more effective, or safer than old treatments and to determine the correct dosage of new drugs. In addition, they provide evidence that a new drug is safe and effective and eligible for marketing by each country's governing body.

Results from clinical trials can lead to the development of medicines that can prevent thousands of deaths each year, and also improve the lives of thousands more people who live with various medical conditions.

There are also a number of possible advantages for people participating in clinical trials. These can include the opportunity to try new treatments that are not offered to the public which may work better than the treatments currently offered, obtaining the clinical trial medicine at no cost (at least during the trial), receiving extensive medical care associated with the clinical trial, and the patient's opportunity of taking a more active role in their own healthcare while helping to expand scientific research.

What are the risks involved in partaking in a clinical trial?

Of course, people who are considering joining a clinical trial should bear in mind that since treatments being studied are new, doctors don't always know what the side effects may be, and some treatments may cause problems or side effects that are unpleasant, serious, or life-threatening.

There is also a risk that the trial medicine may not work, or that the treatment may not work for certain people. In addition, a person may be placed in the control, or reference group, and therefore not receive the trial medicine until after the clinical trial has finished. Also to be considered, is that the study may take more time than would undergoing a regular treatment regime, and that the patient might need to make many visits, have many tests and perhaps need to stay in the hospital.

How long after the clinical trial has concluded will a person have to wait to be given their results? Where are the trial results made available to others, published in journals and presented at conferences?

As well as being reviewed by government authorities such as the Therapeutic Goods Administration, the results of the clinical trials may be reported in the medical press and made available for doctors at medical conferences. The publication of results is done so that doctors can make scientifically valid assessments of the benefits and risks of a new medicine for their current and future patients.

Although the results of the study may be published, nothing that identifies individual patients is released, and all the details of a clinical trial participant's treatment are kept confidential, as patient anonymity is assured.

Your doctor will be notified of the results of the study as soon as they are made available and your doctor should then be able to inform you of the outcomes of the clinical trial. For trials of new management strategies for chronic hepatitis B and C, it is 12 -18 months after completion of treatment in all study participants before the results of the trial are available for discussion and publication. If you participate in a study, it is recommended that you keep in touch with your doctor so that you can find out the results of the study when they become available.