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Overview about clinical trial and human research

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INTRODUCTION

Experiments performed in the laboratory are known as "basic research". The goal of basic medical research is to increase our understanding of normal human biology and diseases, and ultimately to discover and develop new treatments or technologies to improve health. Before newly discovered (potential) treatments can even be considered for testing in humans, however, they will have to undergo more intense laboratory testing and preclinical research. New drugs will undergo several stages of experimentation in vitro (in test tubes) to study their chemical properties. New treatments that have the potential to improve health (therapeutic potential) may then be studied in cells and/or tissues grown in the laboratory in order to study their biological effects, especially their toxicity, and to establish a safe dosing plan for further testing. If they pass this stage, they may then be tested in in vivo (in animals) in order to study the effects in whole living systems and to get a better idea of safe, effective dosing in humans. If the new treatment appears to have therapeutic potential in animals (or healthy/diseased human cells/tissues/organs), appears to be safe, and the risk of side effects appears to be low and minor, it may move into the first phase of clinical trials.

Clinical trials are research conducted in people (healthy participants or patients with a specific health issue) in order to study and test new medical treatments, such as drugs, vaccines, medical devices (e.g. spinal cord stimulators), medical procedures (e.g. surgical procedures), and diagnostic tests. Clinical trials may also be conducted to study new combinations of treatments, or to compare treatments, or to study an already available treatment for a new use (e.g. to trial a drug currently used for depression in patients with chronic pain).

This article will focus on clinical trials for new drugs or medical devices. It will provide an overview of the stages / phases of clinical trials, the regulatory, ethical and safety requirements, who is involved in conducting a clinical trial, what is involved, and what happens after a trial is complete.

Various stages of Clinical trials

Phase-0 (Exploratory / Pilot Study)

Conducted across small population of (10 – 15) volunteers. A small study (pilot) to test how the human body responds to a very small (sub-therapeutic) dose of a drug. This is done in order to explore diagnostic tests or study how drugs or devices work (exploratory study).

Phase-1 (Safety / Tolerability Study)

First testing in humans, primarily to test safety. A drug is given to a small number of healthy volunteers who are closely monitored. The first stage of testing effective doses in humans (healthy humans and/or patients) to establish the safe, therapeutic dose range and identify any side effects. Done in healthy volunteer or in patient population. Involves a sample size of 20-100 patients. The maximum tolerable dose is determined by Dose Limiting Toxicity.

Phase-2 (Exploratory / Dose Ranging Study)

In this phase of clinical trial various dose are being studied to find out a safe and effective dose. This phase is usually conducted with 200-300 population.

Phase-3(Confirmatory)

This phase is conducted to assess the effectiveness and confirm the clinical benefit and safety risks of the treatment for the intended health condition.

Phase-4 (post marketing/surveillance)

This phase is conducted Marketing and safety surveillance of the now approved treatment to monitor its effectiveness, safety and long-term effects in the general population. It usually takes around 10 to 15 years for a new drug to pass through clinical trials and receive market approval.

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Overview of clinical trial design

Control trial: controlled is one in which there are at least two groups of participants – one group receives the new treatment and one group receives a comparison treatment (or no treatment) and is known as the "control" group. To have something to compare the treatment to makes for a much more powerful study with more clinically meaningful results.

In clinical trials that involve patients and healthy participants, the healthy group is the control group. If it is unethical to include healthy controls, the control group may:

- Receive a standard, comparison treatment that is commonly prescribed for the same condition; or
- Receive physical therapy only; or
- Not receive any treatment; or
- Receive a placebo.

Randomization: It is the process of randomly allocating participants to either the treatment or control / comparison groups (also known as "treatment arms"). This is generally performed by a computer program. Randomization ensures that the process of assigning participants to different groups is not biased (i.e. an investigator that decides to put a certain patient into the treatment group because their condition appears particularly bad). Randomization also ensures that the groups are balanced, which makes them more comparable, and that participants have an equal chance of receiving the treatment or control / placebo / comparison treatment.

Blinded study: A controlled trial will usually be "blinded". Naturally, placebo-controlled trials are always blinded. This means that participants are unaware of which treatment they receive until the study is complete. A study is double-blinded if the study investigator(s) are also unaware of which treatment the participants receive. Blinding ensures that the outcomes are not biased by participants' or investigators' preconceptions – that is, what they think the outcome will be if they know which treatment they are receiving. For example, a person who receives a new treatment versus an already available or a standard treatment may think that they will experience more side effects or better results.

Cross over study: In most controlled clinical trials, participants will receive either the new treatment or the control/comparison treatment and that's it. Another word for this is a "parallel" study. In a crossover study, all participants get to experience both the new treatment and the control/comparison treatment. After a certain period of being on the new treatment or the control treatment, participants will swap groups. Usually, a crossover study involves a washout period, during which participants stop taking the treatment or control that they were on, for a certain amount of time in order to "wash away" any lasting effects before swapping treatments. This type of clinical trial is usually much longer than a parallel clinical trial. The main advantage is that participants become their own controls and makes for a better comparison between treatment and control. Participants are also much more likely to join a placebo-controlled trial if they will definitely get to trial the new treatment too.

Ethics and regulation governing clinical trials:

Clinical trials are heavily regulated and must be conducted in accordance with standard ethical guidelines, codes of conduct and national laws. This is to ensure participant safety, protection of human rights and privacy, good clinical practice, responsible research conduct, and quality data collection.

For clinical trials involving a new treatment, an application must first be sent to the national regulatory authority – i.e. the Therapeutic Goods Administration (TGA) in Australia, or the Food and Drug Administration (FDA) in the USA.

All clinical trials, whether for new or established treatments, must be approved by an institutional review board (IRB) or a human research ethics committee (HREC; as in Australia). The board or committee consists of doctors, researchers and members of the community. They will review and discuss the study protocol and all other study documents and forms to ensure that the proposed study is ethical, that the rights and welfare of the participants will be protected, and that the potential risks are minimised and reasonable when weighed against the potential benefits of the study. Once approved, the IRB / HREC will continue to monitor the trial.

Safety in clinical trials:

A clinical trial may be terminated if there are serious safety concerns, or in the event of futility (i.e. there appears to be no benefit associated with the treatment and/or the final results are unlikely to be of any

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significance – basically, it would be a waste of time and resources to continue the trial). On the other hand, a trial may be terminated in the event of overwhelming benefit (i.e. the results so far indicate a substantial statistically significant benefit associated with the treatment), in which case regulatory approval and market-release may be achieved much sooner than normal.

Various Stakeholders involved in clinical trials

a. Investigators-Physicians/Doctors

Clinical trials are conducted by doctors, usually specialists. The lead doctor is known as the principal investigator and any other involved investigative doctors are known as sub-investigators. Qualified clinical research staff may also perform the roles of a sub-investigator. The investigator(s) will supervise or perform the treatment and perform study visits / follow-up consultations. The principal investigator is responsible for ensuring good clinical practice, that the trial is run according to the protocol and safely and that participants receive the appropriate care.

b. Clinical trial coordinators

These are qualified clinical researchers (i.e. research nurses or researchers with a biomedical degree or similar who have clinical experience). They are usually the main point of contact for participants and are present at the majority of study visits. They are involved in recruiting participants and providing them important information about the trial before enrolment and throughout the trial, organizing appointments and medical tests, monitoring participants, and data collection. They may also administer treatment and take blood if qualified and designated to do so by the principal investigator.

c. Other health Professionals

Various other health professionals may be involved in clinical trials, whether actively involved in the study or as external support. Examples include:

- General practitioners or specialist physicians – may inform their patients about appropriate clinical trials, provide advice on clinical trial participation, support their patients during a clinical trial;
- Allied health practitioners (i.e. psychologists, physiotherapists);
- Pathology and medical imaging staff (radiologists);
- Pharmacists;
- Company engineers who perform routine programming / maintenance for medical devices.

d. Sponsors

Clinical trials may be industry sponsored, non-industry sponsored or investigator-initiated. The sponsor may be a government agency, a pharmaceutical, biotechnology or medical device company, a charity, research organization, hospital, university or an individual.

e. Monitors

These are people contracted or employed by the sponsor tasked with overseeing the trial to ensure that it is conducted and reported in accordance with regulatory requirements. They perform site initiation visits, inspections and data and safety monitoring, amongst other tasks.

Steps in clinical trials:

1. Recruitment : Recruitment of clinical trial participants may be conducted in several ways, for example:

- In collaboration with doctors who may inform potentially suitable patients and refer them to a trial site;
- Advertisements in newspapers, radio, bulletin boards, posters, flyers, social media, etc;
- Community information sessions or events;
- Contacting past participants or people who have registered their interest to participate in clinical trials and have joined a research database.

People who find clinical trials online may be directed to a survey that is designed to briefly assess their suitability to participate. Others may be pre-screened via telephone. The full screening process is conducted at the trial site.

2. Screening: To be eligible to participate in a clinical trial, potential participants must attend the site for a screening visit. They must meet set “inclusion criteria” and not meet any “exclusion criteria”. These often-strict selection criteria are put in place for safety purposes and to minimise variation in the study group(s) that might influence the results. Clinical trials in later phases may have less strict selection criteria.

3. Eligibility criteria may include:

- Age;
- Sex;

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- Health condition;
- Symptom presentation;
- Duration of illness or symptoms;
- Other medical history;
- Treatment history.

4. Common exclusion criteria include:

- High BMI
- High blood pressure.
- Comorbid conditions (e.g. diabetes);
- Use of excluded medications;
- Pregnant or breast-feeding mothers;
- Inability to undergo certain procedures or tests;
- Living too far away from the trial site.

Potential participants will be asked to complete questionnaires designed to assess their health status or health condition and determine whether the study is suitable for them. They may also need to undergo a physical examination and medical tests (i.e. blood tests, X-rays, MRI) in order to determine their eligibility.

In the event that a person is found not to be eligible for the study, they will be told promptly and may then be asked if they would like to remain on the site's research database where they may be contacted about potentially suitable trials in the future.

Consent and enrollment

Before an eligible person can be enrolled into a clinical trial, they must first meet with the investigator to discuss the trial and give "informed consent". This begins at the screening visit. Informed consent is a legal and ethical requirement and is described below.

At the screening visit, the investigator and coordinator will provide important information on the clinical trial in the form of a study brochure or information sheet and will answer any questions or concerns. They should ensure that the potential participant has an adequate understanding of the trial, its purpose, the procedures, the risks and potential benefits of participation, and their requirements and rights as a participant. The study information may be taken home and discussed with others (family, friends, doctors). If the person decides to participate in the trial, they will need to return to the site to meet with the investigator and sign the consent document. This document is not a contract, it represents an agreement to participate in the trial and an understanding of what it will involve. Participants may withdraw their consent and leave the trial at any time.

Important points to consider:

Informed consent is more than just the signing of a document and pre-enrolment discussion, it is an ongoing process;

Participants should feel free to ask as many questions as they need to before and after signing the consent document and during the study;

If there are any changes to the study, participants will be informed and may be asked to re-consent before continuing the trial;

Many patients have the misconception that participating in a clinical trial will improve their condition. It must be made clear that this is not guaranteed;

Patients with debilitating conditions, cognitive impairments, limited literacy skills, non-English speakers, the elderly, and so forth, should be accompanied by a family member/carer. Modified strategies and more time and effort may be required in order to adequately complete the informed consent process.

Starting of study treatment

Eligible participants who provide informed consent will be booked in for a baseline visit. At this visit, the participant will meet with the investigator and coordinator where they can continue to discuss the trial. The participant will be asked to complete sponsor study documents, medical information forms and questionnaires to assess health, symptoms, etc. The participant may also be required to undergo a physical examination and medical tests, such as blood tests, X-rays, MRI, etc. The information collected as this visit forms the baseline data. Participants may also receive a diary to take home in which they should record information such as any side effects, medication changes and health condition changes, should they occur.

Following the collection of baseline data, the participant will receive the trial treatment. This may be in the form of pills to be taken as directed, an injection that is performed at the site or that is self-administered at home, or an external medical device that is worn by the patient. The investigator/coordinator (and/or a company engineer for medical device trials) will educate the participant on how to take or use the treatment.

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Follow Up

Participants will be required to attend regular, scheduled follow-up study visits. The number of visits and length of time between visits depends on the treatment and the trial design. During these visits, more data will be collected in the form of questionnaires, and perhaps physical examination and/or blood tests and/or medical imaging. Medical device trials may require extra time or visits for device programming.

Reporting of Adverse events

Whilst clinical trials are carefully designed, staged and controlled in order to minimise the risks associated with testing new treatments, adverse events are not uncommon. Even medications already on the market are often associated the side effects. Adverse events include side effects or reactions to the study treatment, any events or illnesses that occur during the trial, even if it is uncertain whether they are or are not related to the study treatment, worsening of a health condition, and so forth.

Just as any prescribing doctor and pharmacist will advise patients of the potential side effects before taking medications, investigators and clinical staff should ensure that potential participants are aware of the potential risks associated with the clinical trial.

If any adverse event occurs, participants should notify the clinical staff and schedule a visit as soon as possible, even if they've already sought medical help elsewhere. The adverse event will be thoroughly documented and the investigator and clinical staff will follow the event until it is resolved. If the participant decides to withdraw from the trial, the investigator will continue to see them, providing the necessary medical care in order to resolve the adverse event. On the other hand, the investigator may decide to withdraw the participant if there is serious concern. All adverse events will be reported to the sponsor and the relevant authority and appropriate safety measures will be taken.

Medical device trials

If the treatment is a surgically implanted device, the coordinator will arrange the procedure booking. The procedure will take place at a designated hospital and will be performed by the investigator. Usually, the participant will need to return to the trial site shortly after to have their device set up by the engineer/programmer.

In the case of a neuromodulation device trial (i.e. spinal cord stimulator) the participant will be required to trial the device for around a week, during which they will complete a diary to record the effects of trial device. The trial device is partially implanted – the stimulating leads are implanted whereas the pulse generator is worn externally. After the trial, the device is completely removed and the diary is assessed to determine if the device provided clinically significant benefits to the participant. If the trial was a success, the participant will be booked in for their implant procedure, during which the entire device is surgically implanted. Usually about a week later, the patient will return to the site to have their device activated by the engineer/programmer, who will adjust and optimise the device program parameters.

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