

MODULE 3

Science and research

In this module we discuss how researchers develop and test new drugs and vaccines. In Module 4 we will look at how this applies to HIV vaccines.

In this module we discuss:

1. What do we mean by science and research?
2. What is the modern scientific approach?
3. What is clinical research?
4. What types of clinical research do we get?
5. What happens in each stage and phase of clinical trials?
6. What is a research protocol?
7. What guidelines and laws do clinical researchers follow?
8. Who are the most important parties involved in approving, running and quality assurance of clinical trials?





WORD BOX

Science:

The observation, identification, description, experimental investigation, and theoretical explanation of events or facts that can be observed.

Research:

Scholarly or scientific investigation.

Scientific research:

Scholarly or scientific investigation using the scientific method.

Reliable:

Giving the same or similar results in different experiments.

Accurate:

Reflects the truth and is precise.

Reproducible:

Can be tested and repeated many times getting the same or similar results.

Technology:

The practical use of scientific knowledge in industry and everyday life.

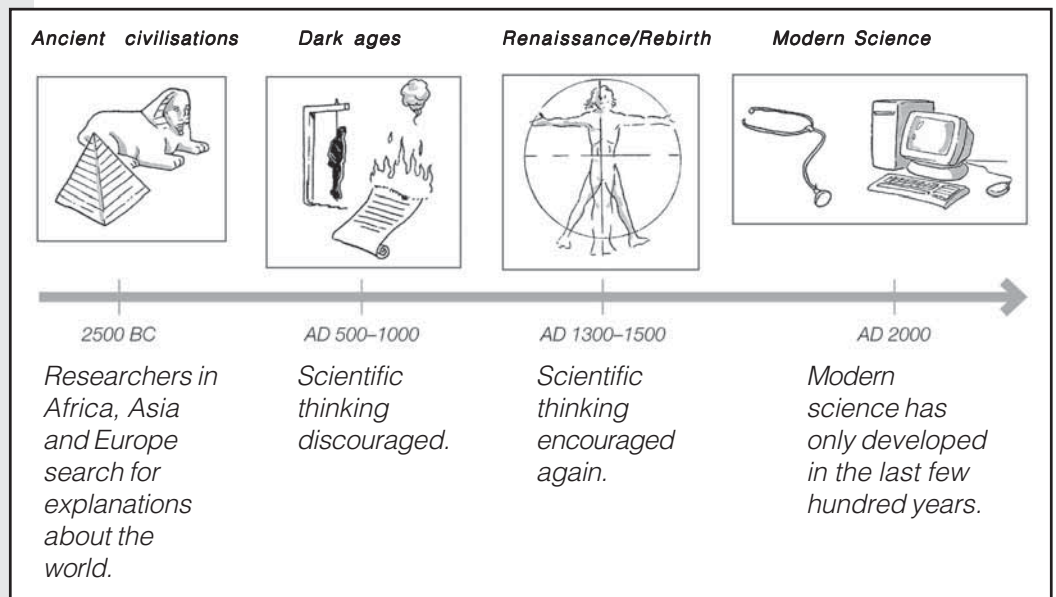
1. WHAT DO WE MEAN BY SCIENCE AND RESEARCH?

There are many different ways we can get knowledge about our world – from our parents, schools, books, radio, newspapers, television, our community leaders, our experiences, and through **scientific research**.

Science is a way of getting the most **reliable, accurate** and up-to-date knowledge and information about the world and universe around us. It helps us answer questions about what happens in the world and why it happens. Scientific knowledge also helps us improve our health and our lives.

Researchers follow certain procedures and steps to get the most reliable, accurate and **reproducible** information which can be tested and retested many times. These steps or procedures are called the scientific method.

The history of science



Timeline of how science developed



DID YOU KNOW?

Scientific knowledge is often used to develop new products and **technology** to help us solve problems in our everyday life. An example of technology is the use of vaccines to prevent diseases like smallpox and polio. These vaccines are based on scientific knowledge gained through clinical research.





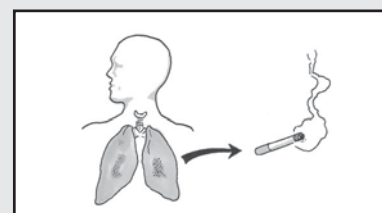
2. WHAT IS THE MODERN SCIENTIFIC APPROACH?

Researchers follow certain steps when they study a problem to find the most reliable information they can. They then use this information to find answers to common problems, for example, answers to health problems like TB, HIV and AIDS, and malaria. The steps researchers use make up what we call the modern scientific approach or method.

Step 1: Researchers make an observation

Researchers see something happening in the world and check to see if it happens again, and again and again.

For example, researchers see that many patients at a Cape Town clinic who have lung disease, also smoke. They see the same pattern in two other clinics in other patients with lung disease.



Step 1: Researchers make an observation.

Step 2: Researchers ask a question about what they have observed

Researchers ask questions in a way that helps them plan their research and find answers to the problem.

For example, researchers ask: *Are there more cases of lung disease in people who smoke, than in people who do not smoke?*

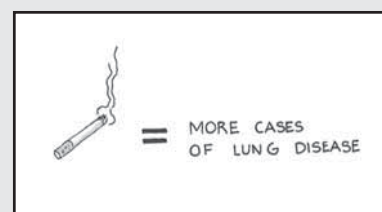


Step 2: Researchers ask a question about what they have observed.

Step 3: They put the question into a statement called a hypothesis

Researchers turn the question into a statement called a hypothesis. The hypothesis includes a possible explanation to the problem that they have seen.

In our example, researchers might develop this hypothesis: *There are more cases of lung disease in people who smoke than in people who do not smoke.* The hypothesis gives the possible explanation for the health problem that they observed, e.g. smoking can explain the cases of lung disease.

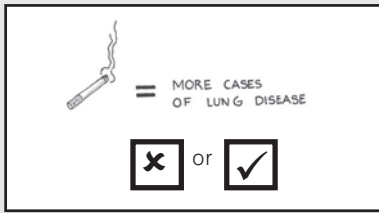


Step 3: They put the question into a statement called a hypothesis.

WORD BOX

Hypothesis:

A statement that gives a possible explanation for an observation or a happening in the world.

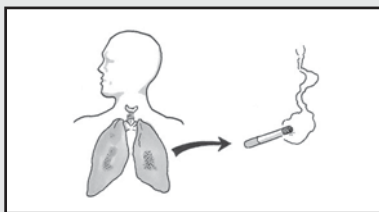


Step 4: Researchers do an experiment or study to prove whether the hypothesis is correct or not.

Step 4: Researchers do an experiment or study to prove whether the hypothesis is correct or not

Researchers collect all the information they can in a certain way to see if their hypothesis is correct or incorrect.

In our example, researchers study a group of 200 people from three clinics. There are 100 smokers and 100 non-smokers. Researchers want to see if the smokers get lung disease more often than the non-smokers. They do regular chest X-rays on the group over five years and find that 5 out of 100 (5%) smokers get lung disease, compared to 1 out of 100 (1%) non-smokers. This difference is not large enough to prove that smoking causes lung disease.



Step 5: If the study shows that the hypothesis is correct, researchers may repeat the experiment to see if they get the same or similar results.

Step 5: If the hypothesis is correct, then the researchers may repeat the experiment to see if they get the same or similar results.

The same or a different group of researchers repeat the experiment to compare if they get the same or similar results each time. If they do, it means they can be sure of the original findings.

So, if the results had shown that smoking causes lung disease, the researchers would repeat their lung disease experiment in another set of clinics. They also would work with other researchers in a different town who do the same experiment in their clinic at the same time.



Step 6: Researchers tell others about their results.

Step 6: Researchers tell others about their results

Researchers publish their results in scientific and medical magazines and journals to tell others about their findings. Other researchers can then test the findings to see if they are reliable and accurate – whether they get the same or similar results.

DID YOU KNOW?

It is very important that researchers work out a big enough sample size for their studies. *This is to make sure that the results are not due to chance, and that they can be applied to the broader population.*

For example, researchers do the lung problem study in a small sample size of 20 people (10 smokers and 10 non-smokers). They find that 5 out of 10 smokers get lung disease compared to only 1 out of 10 non-smokers. They repeat the study in a much bigger sample size of 200 people (100 smokers and 100 non-smokers) and find that only 5 out of 100 smokers get lung disease compared 1 out of 100 non-smokers.

The results from the bigger sample size represents the broader population better. This tells them that only 5% of smokers get lung disease compared to 1% of non-smokers. The results from a small sample size could simply be due to chance. They cannot be applied to the general population. For example, we cannot say that 50% (5 out of 10) of all people who smoke will get lung disease.



Scientific research is any detailed or careful investigation using the scientific method. **Clinical research** is one type of scientific research.

2. WHAT IS CLINICAL RESEARCH?

Clinical research is research done in humans. It tries to answer questions about human health and disease. It must be done in the most **ethical** and respectful way possible because it involves people. People's human rights must also be respected.

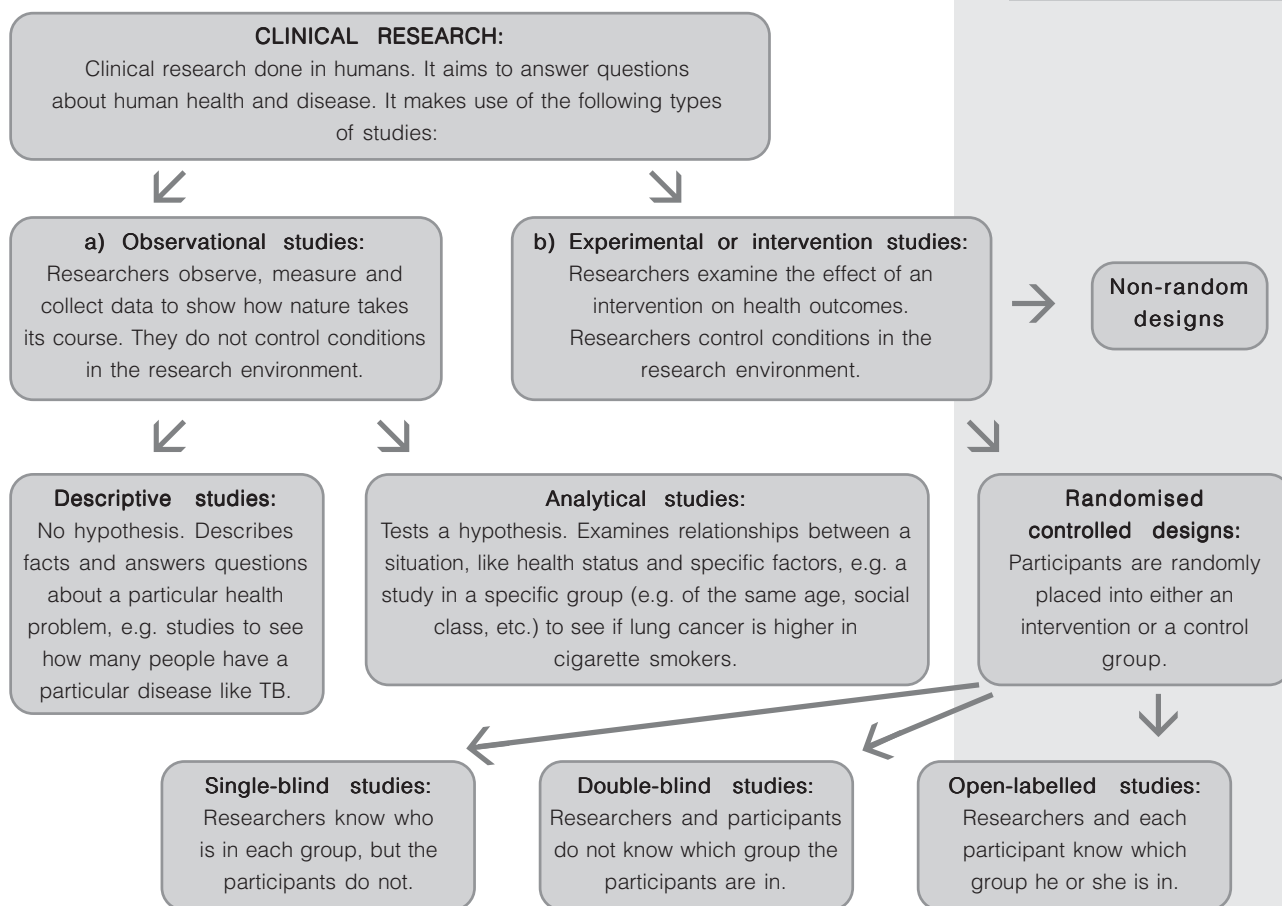
The chart below shows the two main types of clinical studies. Each type is further divided into different kinds of studies that researchers can use. Most drug and vaccine research uses experimental or **intervention** studies.

WORD BOX

Clinical research:
Research done in humans to try to answer questions about human health and disease.

Ethical:
Doing things in ways that are acceptable, 'right', fair and just.

Intervention:
Anything that is implemented to alter the outcome of a health problem. For example, implementing the use of a vaccine to prevent people getting flu.





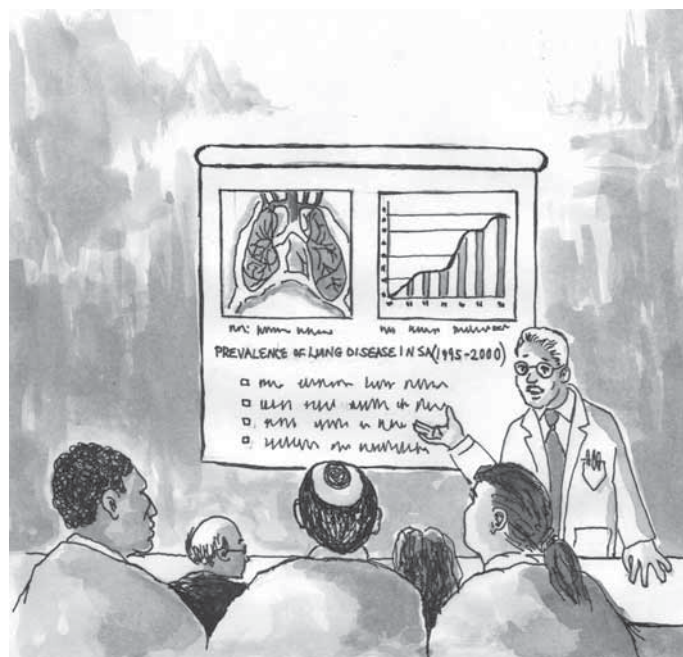
a) Observational studies

Here researchers observe, collect data and describe how nature takes its course, e.g. how a health problem develops. They do not control conditions in the research environment or examine the effect of an intervention, like a drug or vaccine, on the health problem. There are two kinds of observational studies:

Descriptive studies: In these studies, researchers do not have a hypothesis. Rather, they describe facts and answer questions about specific health problems. For example, they ask: How large is the health problem, e.g. how many cases of HIV are there? Who has the problem? In what part of the country do they live?

Analytical studies: In these studies, researchers compare two different groups of people, e.g. smokers and non-smokers, to see if there is a link between an outcome (e.g. their health status) and specific factors (e.g. smoking). *For example, researchers might ask: Are there more cases of lung disease (health status) in people who smoke than in people who do not smoke? (Smoking is the specific risk factor.)*

Analytical studies involve testing a hypothesis. These studies can look at **risk factors** – factors that researchers think can put a person at risk of developing a certain disease. They can also look at **protective factors** – factors that researchers think may protect people from developing a certain disease.



Researchers observe how common lung disease is in South Africa from 1995–2000. This would be a descriptive study.

WORD BOX

Risk factors:

Factors that put a person at risk of developing a certain disease or health problem.

Protective factors:

Factors that protect a person from developing a certain disease or health problem.

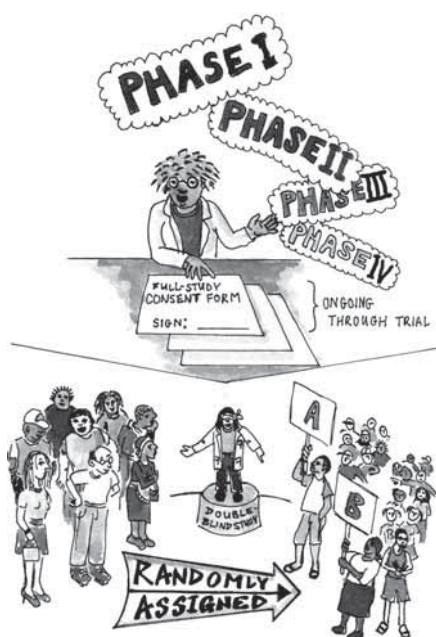


b) Experimental or intervention studies

Here researchers study the effect of an intervention on a health problem. For example, they give a drug or vaccine to see if it improves a health problem, e.g. does it help to treat someone's asthma or diabetes? The research takes place in a controlled environment – they control some of the conditions under which **trial participants** are studied. There are different kinds of intervention study designs. We are most interested in the randomised control trial (RCT) design.

In the RCT design, trial participants must meet certain requirements or criteria, for example, they must be between 18 and 45 years old and healthy. Those who qualify are **randomly** placed into one of two groups, including:

- **The intervention group:** This group receives the intervention, e.g. the drug or vaccine.
- **The control group:** This group does not receive the intervention. They get a different intervention (e.g. another drug or treatment that is known to work), or a **placebo**.
 - A placebo looks the same as the intervention, but it is **inactive** – it is safe and has no action in the body.



RCTs make the best intervention study design because researchers can clearly compare the results in the intervention group to the results in the control group to see what effect the intervention has. If the health condition that the intervention tries to treat improves significantly or much more in the group that got it than in the group who did not, then researchers will know that the intervention is working. This is because all other research conditions are the same for the two groups, except that one group got the intervention and the other group did not.

WORD BOX

Trial participants:
People participating in the study.

Randomly:
By chance.

Intervention group:
The group that receives the intervention.

Control group:
The group that does not receive the intervention.

Placebo:
Looks the same as the intervention, but is not active – it does nothing, e.g. like the sugar tablets in a box of the Pill (contraceptives).

Inactive:
It has no action or effect on the body.



The intervention and the placebo look the same, but the placebo is inactive.



There are also different RCT study designs:

- **Open-labelled study:** Here trial participants and the researchers know which participants are in the control group and in the intervention group.
- **Single-blind study:** Here the researchers know which group the participants are in, but the trial participants do not know.
- **Double-blind study:** Here both the researchers and the trial participants do not know which group the trial participants are in.

In Module 4, we will see how HIV vaccine clinical trials use the double-blind, placebo-controlled RCT design.



DID YOU KNOW?

Researchers only use a placebo if there is no effective treatment, drug or vaccine for the health problem being studied. It is unethical not to give the effective treatment. But, when researchers use a placebo they must make sure that the trial participants do not know whether they will get the intervention or the placebo. We say that the trial participants are 'blinded' so as to avoid 'the placebo effect'. Any improvement in the health of the intervention group will then be due to the intervention only.

What is the placebo effect?

Many health problems get better on their own. Researchers also know that the mind is a powerful tool and that sometimes if people know that they are getting some kind of treatment, then they think it will make them better – and they get better, not because of the drug but because of the power of their mind over their body. This is called the placebo effect.



In a 'double-blind' RCT the 'blind' is usually only broken at the end of the study, or in an emergency.



3. WHAT HAPPENS IN EACH STAGE AND PHASE OF CLINICAL TRIALS?

There are four stages that researchers go through to develop a drug or vaccine for humans:

Stage 1: Discovery: Basic research and development in the laboratory.

Stage 2: Exploration: Testing the drug or vaccine on animals.

Stage 3: Clinical trials in humans.

Stage 4: Public implementation: Licensure and manufacture.

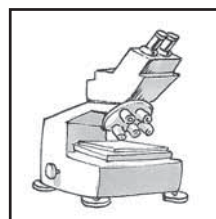
} Both stages 1 and 2 form part of pre-clinical studies.

Stage 1: Discovery

Here there is research and development in the laboratory.

Researchers try to understand a specific disease and/or they try to **isolate** the germ that causes the disease.

They try to understand what the germ is made up of and how it works. Using this information, researchers develop a potential drug or vaccine in the laboratory to prevent or treat the disease. If the germ is complicated, this stage can take a long time.



Stage 1: Discovery

Stage 2: Exploration

Researchers test the drug or vaccine on small animals, like mice.

They see how safe the drug or vaccine is and what kind of response the animal develops to it. If the information is hopeful or promising, then they do tests on larger animals. To go on to Stage 3, the information from Stage 2 must show that:

- The test drug or vaccine is safe – it produces very few, or no **adverse events** in the animals.
- It is not **toxic**.
- It produces a promising response in the animals.



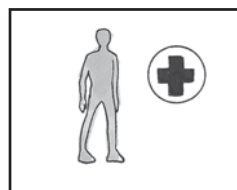
Stage 2: Exploration

If results from the pre-clinical studies look promising, **sponsors**

can send a research plan (called a protocol) to the country's regulatory body for approval to do clinical trials in humans. In South Africa this body is the Medicines Control Council (MCC). The Sponsor must also get approval from other parties, e.g. Research Ethics Committees (RECs), before the trial can begin.

Stage 3: Clinical trials in humans

There are four main phases of clinical trials, as we can see in the tables on the next few pages.



Stage 3: Clinical trials in humans

WORD BOX

Implementation:
Use.

Licensure:
Licensing the drug or vaccine for public use.

Isolate:
To identify and separate or remove a specific germ from, e.g. a blood or tissue sample.

Adverse event (AE):
Any unpleasant or unintended medical sign, symptom, or disease, in a patient or trial participant who is given a pharmaceutical product. The AE is not necessarily caused by the pharmaceutical product.

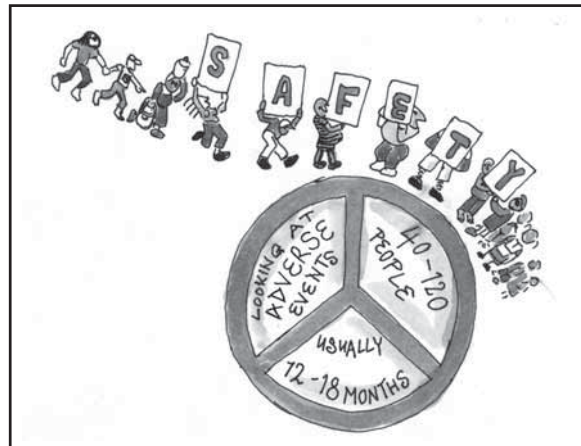
Toxic:
Poisonous.

Sponsor:
The company, institution or organisation that takes responsibility for beginning, managing and/or financing a clinical trial.



Phase I: Safety

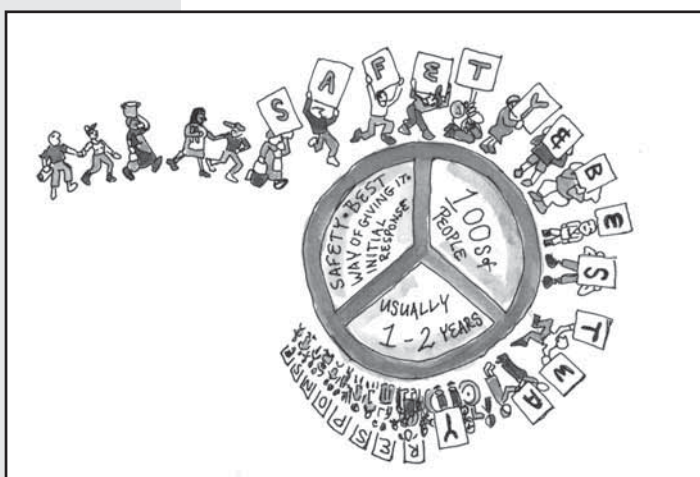
Aims	How many participants?	How long?
The aim is to test if the drug or vaccine is safe.	40 – 120 people	Usually 12-18 months



Phase I: Mainly for safety

Phase II: Safety, to start to see if it causes a response, and the best way to give it

Aims	How many participants?	How long?
<ul style="list-style-type: none"> ■ The aim is still to test for safety and also to see if the drug or vaccine causes the response researchers want to see. ■ Researchers also study the best way to give the drug or vaccine, e.g. by injection, pill, syrup; how much to give; and how often to give the drug or vaccine. 	100s of people	Usually 1-2 years
There can be a phase IIb trial which is similar to a phase III trial, but with fewer people. This is less costly than doing a phase III trial. The knowledge gained can be used to guide future research on the drug or vaccine.	A few 1 000 people	

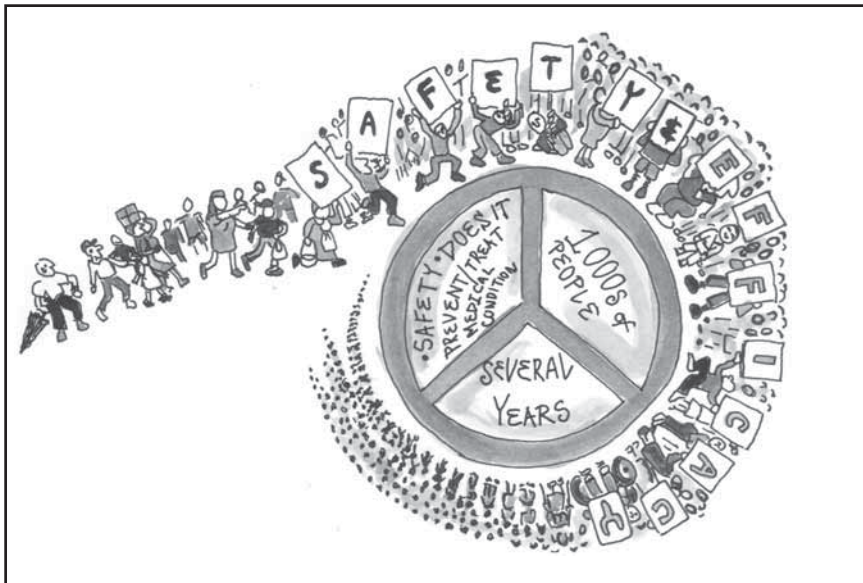


Phase II: Safety, to start to see if it causes a response, and the best way to give the drug or vaccine



Phase III: Safety, and whether it works

Aims	How many participants?	How long?
The aim is to test if the drug or vaccine is effective, i.e. whether it works to prevent or treat a medical condition, and always to test for safety.	Several 1 000s of people	Many years



Phase III: Efficacy, and always safety



Pregnant women should only be in the research if it is safe for them and their baby.

DID YOU KNOW?

It is important for women to be included in clinical trials so that they benefit from the latest research. If women are not included, we will not know if the research results can be used for them. Pregnant women should only be included in the research if it is safe for them and their baby. They must completely understand all the risks and benefits involved, and researchers must make sure that the research cannot harm the unborn baby.



Note the following about phase I-III clinical trials:

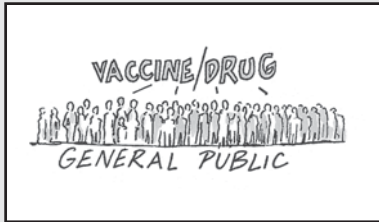
- Each phase of trials has certain entry requirements or criteria that participants must meet. For example, they must have bad asthma and be living in Johannesburg.
- The phases run in exact order from I-III.
- Researchers cannot move from one phase to the next unless the results of the previous phases show that the drug or vaccine is safe and promising. The research plan for the next phase must be submitted, **reviewed** and approved by, e.g. the scientific and ethical review bodies before the trial can start.

WORD BOX

Review:
Read, study, analyse, assess, evaluate.



Stage 4: Licensure



Phase IV: Performance on a large scale

Stage 4: Public implementation

The ideal outcome of a phase III clinical trial is a drug or vaccine that is safe and effective. In South Africa, if a drug or vaccine is successful in a phase III trial, researchers can apply to the MCC to obtain a licence for public distribution. Once a drug or vaccine is licensed, mass produced and ready for public use, then phase IV studies can begin. These are called post-licensure or field studies.

Phase IV: How does the drug or vaccine perform in the general public?

Aims	How many participants?	How long?
Researchers check how well the drug or vaccine works when it is given to the general public in real-life conditions.	The general public is involved	Long-term and ongoing

During field studies, the regulatory authority of the country should keep track of the drug or vaccine and any rare but serious adverse events (SAEs) that it may cause. Often SAEs only show up when a drug or vaccine is used on a very large number of people, e.g. tens of thousands of people.

For example, in 1998 a vaccine was licensed in the United States of America (USA) to prevent disease caused by a virus called the rotavirus. The rotavirus gives babies diarrhoea and causes about 440 000 deaths a year around the world. Nine months later the immunisation programme was stopped because the vaccine caused a rare AE called **intussusception**.

WORD BOX

Intussusception:

A problem in the intestine where one part of the bowel slides into the next.



DID YOU KNOW?

A drug or vaccine that does well in a phase III trial may not do as well during phase IV. This can be because of poor storage facilities – many drugs and vaccines need to be kept in fridges to work properly – or because of incorrect use of the drug or vaccine, etc. These problems can be solved by, e.g. giving health care providers more training, buying or building better storage facilities, etc.



DID YOU KNOW?

The research protocol includes a statement that says that the researchers agree to do the trial according to the protocol, **Good Clinical Practice (GCP)** and other **regulatory requirements**.

GCP is the minimum standards or requirements that must be followed in a clinical trial. These standards tell us how the trial should be carried out, monitored, analysed and reported. This ensures that the data and results from the trial are reliable and accurate. GCP also aims to protect the rights, integrity, and confidentiality of trial participants.

In South Africa, local GCP requirements are written into a document called *The Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa*. Researchers in South Africa must also follow these regulatory requirements and guidelines:

- the *Constitution* (1996),
- the *National Health Act* (2003), and
- the *Department of Health Guidelines: Ethics in Health Research: Principles, Structures and Processes* (2004).

Research that is done or funded by the South African Medical Research Council (MRC) must also follow the *MRC Guidelines on Ethics for Medical Research* (2002). Other guidelines can also apply to research into a specific health issue, e.g. HIV.

The documents on GCP and the regulatory requirements can be found on the Government website: www.info.gov.za/documents/index.htm, the Department of Health website: www.doh.gov.za/docs, and the MRC website: www.sahealthinfo.org/ethics/index.htm

WORD BOX

Good Clinical Practice (GCP):

The minimum standards for how a trial must be designed, carried out, monitored, analysed and reported.

Regulatory requirements:

Generally in South Africa this means all relevant laws, e.g. the *National Health Act* (2003), that apply to approving, running and quality assuring clinical trials.

CASE EXAMPLE

Dr Duma decides to help drug company X test a new drug for diabetics. He asks Amanda, who is one of his new patients who has diabetes, if she wants to join the trial for this new drug. Amanda is eager and agrees to take part. However, she has some worries and asks Dr Duma to tell her more about the drug and how it will be tested on her. Unfortunately Dr Duma has not read the protocol well and is too busy. He gives her a brochure on the drug and tells her that he will see her next week. Amanda finds the brochure difficult to understand. However she is concerned because her diabetes is very bad and she needs to try whatever she can to treat it. So she keeps quiet and agrees to join the trial.

Think about / discuss:

- What does Amanda feel like after her experience with Dr Duma?
- Why is Dr Duma doing this study?
- What guidelines and procedures should Dr Duma be following to ensure that the research including Amanda is scientifically, ethically and legally correct?



5. WHICH PARTIES ARE INVOLVED IN CLINICAL TRIALS?

There are many parties involved in approving, running and quality assuring clinical trials. The following table shows which parties are involved in these different processes:

NOTE:
We look at CAGs in more detail in Module 7.

Parties involved in APPROVING clinical trials.	Parties involved in RUNNING clinical trials.	Parties involved in QUALITY ASSURANCE of clinical trials.
The Sponsor	The Sponsor	The Sponsor
The Regulatory Authority, e.g. the Medicines Control Council (MCC)	The Regulatory Authority, e.g. MCC	The Regulatory Authority, e.g. MCC
The Research Ethics Committees (RECs)	RECs	RECs
The Department of Health with whom the clinical trial must be registered.	Trial site staff, e.g. the PI, the trial site co-ordinators, doctors, nurses, counsellors, laboratory technicians, administrative staff, community outreach team, etc.	The Monitor
	The Community Advisory Group (CAG)	The Auditor
		The Independent Data Monitoring Committee (IDMC) or Data and Safety Monitoring Board (DSMB)
		The CAG

Although we look at the role of these parties in Module 4, here is a short description of some of the most important ones:

- **The Sponsor** is the organisation that starts, manages and/or finances a clinical trial. They take overall responsibility for designing the trial, and submitting the protocol and trial reports to the regulatory authority/ies and the RECs for review. The Sponsor ensures supply of the products to be used in the trial and is responsible for safety evaluation of the products throughout the trial. They appoint the Principal Investigator/s (PI), the Monitor, and sometimes the Auditor and the Data Safety Monitoring Board (DSMB).



- **The Regulatory Authority/ies** is an independent body set up by government to regulate or control activities in an area. In South Africa, an example of such a body is the Medicines Control Council (MCC). They regulate the area of medicines by applying certain rules and standards. They do a scientific review of the research protocol to decide whether to approve the clinical trial. They also evaluate how a trial is carried out, and can inspect the trial sites. They can stop the trial.
- **The Research Ethics Committee (REC)** is an independent committee of the institution/s that takes part in the research. It is made up of academics and community representatives, who review the research protocol and decide whether to approve it from an ethics point of view. They also review trial progress and safety reports to address ethical issues that occur.
- **The trial site team** is usually made up of the Principal Investigator (PI), the trial site director and/or co-ordinator, medical officers (doctors), pharmacists, trial nurses, counsellors, a community outreach team, data managers, social scientists, administrative staff, and laboratory technicians.
 - **The Principal Investigator (PI)** is usually a medical doctor and takes overall responsibility for the trial.
- **Laboratories** run tests on samples collected during the trial, e.g. blood counts, and so on.
- **The Monitor** oversees and reports on the progress of a trial.
- **The Auditor** is an independent party who does an in-depth evaluation of how the trial is carried out.
- **The Independent Data Monitoring Committee (IDMC)**, or Data and Safety Monitoring Board (DSMB), is an independent party that reviews data that is collected at different times during the trial.
- **The Community Advisory Group (CAG)** is a group of volunteers who live in the areas from which trial participants are recruited. They represent the community interests and should be part of making decisions about the research that affect the community. They encourage community involvement in the research and try to ensure that community concerns are addressed.

These parties often interact with each other. Please see page 75 in Module 4.



Stage 1: Discovery



Stage 2: Exploration



Stage 3: Clinical trials in humans



Stage 4: Licensure



Phase IV: Performance on a large scale

- There are four separate stages to developing a drug or vaccine:
Stage 1: Discovery: Basic research and development in the laboratory.

Stage 2: Exploration: Studies in animals.

Stage 1 and 2 form part of the pre-clinical studies.

Stage 3: Clinical trials in humans.

- a) **phase I** – tests mainly for safety;
- b) **phase II** – still tests for safety, the best way to give the drug or vaccine, and to see whether the drug or vaccine causes a desired response; and
- c) **phase III** – tests mainly for efficacy and always for safety.

There may be a **phase IIb** trial. This is similar to a **phase III** trial, but with fewer people. It is less costly than doing a phase III trial. The knowledge is used to guide future research on the drug or vaccine.

Stage 4: Public implementation: Licensure and large-scale manufacture, followed by **phase IV** studies.

Phase IV studies look at how the drug or vaccine performs once it goes into public use.

- Before researchers can conduct a clinical trial or study, they must write and submit a research protocol to the relevant regulatory bodies, e.g. the MCC. A protocol is a detailed plan. This plan provides a list of steps and procedures that guide the way a research study is to be carried out. It is the overall responsibility of the Sponsor to submit the protocol for approval.
- There are several legal, ethical and clinical policies and guidelines that must be followed in the development of a research protocol for clinical trials in South Africa.
- There are different parties involved in approving, running and quality assuring clinical trials.