Chapter 12

Health research and ethical principles
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12.1 Why do we need health research?

This chapter aims to provide an introduction to the nature of health research, as well as the legal and ethical issues that concern research into health. These issues, however, are complex. There are still debates about the duties created by law and ethics in some areas of health research. The chapter also provides information on the institutions (and their policies) that govern research.

Overcoming life-threatening diseases

The history of humankind is in part a history of our struggle to overcome life-threatening disease. In addition to day-to-day illnesses, major epidemics such as the Black Death in Europe in the 14th century, the global flu pandemic of 1918 and HIV/AIDS today have killed millions of people.

But unlike the past, we now understand much more about the causes (and treatment) of ill-health and disease. In the 20th century particularly, medicine has made great advances – diseases such as smallpox and polio have almost been eradicated. But finding more effective ways to treat old diseases and preparing for new disease mean that medicine still has a lot more to learn.

DANGERS POSED BY NEW MICROBES

In early 2003, for example, a new virus called Severe Acute Respiratory Syndrome (or SARS) caused over 800 people to die, mainly in China and Asia. There was a fear that SARS, caused by an airborne virus, could spread all over the world and turn into a deadly epidemic in countries like South Africa, where millions of people have compromised immune systems because of HIV infection. HIV was itself not known until 25 years ago.

SARS and HIV remind us that new microbes (such as bacteria and viruses that cause disease) are emerging constantly and spreading at a faster rate than any time in history. Various factors contribute to this rapid spread: environmental and ecological degradation, squalid conditions of poverty in which many people live, and the collapse of public health systems in many poor and developing countries.

In her groundbreaking book entitled The Coming Plague: Newly Emerging Diseases in a World Out of Balance, Laurie Garrett estimated that more than 21 million people were living in conditions “ideal for microbial resistance”. She described these conditions as being when people are “denied government representation that might improve their lot; starving; without safe, permanent housing; lacking nearly all forms of basic health care and sanitation”.

Different approaches to medicine

There are different approaches to medicine, and the history of medicine goes back many centuries. In South Africa, many people practise traditional medicine that generally uses natural substances such as herbs to treat illness. This is also known as experiential medicine, where curative substances are identified as a result of an accumulation of observations about their effect.

For more on traditional and alternative health care, see Chapter 7.

In contrast, clinical (or so-called “Western”) medicine studies the make-up of bacteria and viruses in laboratories in order to try to discover chemical agents that can be used to counteract them. This is also called biomedicine or evidence-based medicine, where chemicals are tested – in the laboratory, then on animals and later on human beings – to see if they work.

Understanding medicines

Medicines are substances that aim to prevent or treat a disease. Modern medicines are usually made out of chemicals or substances extracted from natural things like trees or plants. They can be taken orally as pills or liquid, inhaled or through injections. The part of a medicine that treats illness is known as the active pharmaceutical ingredient.

**TYPES OF MEDICINES**

- Medicines that prevent the development of an illness are called prophylactics. Co-trimoxazole (an antibacterial medicine) is often prescribed for people living with HIV/AIDS to prevent pneumonia. Antiretrovirals, usually prescribed to treat HIV infection, are also used as prophylaxis to prevent HIV infection following sexual assault. This is called post-exposure prophylaxis (or PEP).

- Antibiotics are medicines that destroy or stop the growth of bacteria in or on the body. Antifungals are used against fungal infections (such as athlete’s foot), with antivirals being prescribed for viruses (such as herpes). Antiretrovirals are a specific subgroup of antivirals used against diseases caused by retroviruses (such as HIV).

- Vaccines are medicines that prepare a person’s immune system to protect the body from a cause of illness. They are usually made from an antigen that causes diseases, but with the disease-causing agent removed or killed. They cause the body’s immune system to react to the antigen and develop antibodies to fight the invading microbe. This creates protection for when the body is attacked by a real virus.
Need for new and better medicines

Chapter 1 explains how factors that influence health are political as well as microbial. Where there is government corruption, where people live in poverty, or where more is spent on arms than on health care, there will be disease. Therefore the fight for better health care is necessarily also a fight for better governance. But the struggle for better health cannot rely solely on campaigns to end poverty and corruption or to improve people’s social conditions.

Most diseases have a pathological cause. In other words, micro-organisms such as bacteria and viruses are the causes of most illnesses. Only through the conducting of clinical trials and other types of research are scientists able to develop new medicines to counter microbes causing known diseases, and to deal with newly emerging microbes causing illnesses like HIV and SARS.

There is also a need to discover new drugs or to replace old medicines, such as those antibiotics in respect of which bacteria have developed resistance. By resistance, we mean that the overuse or incorrect use of certain antibiotics has helped microbes to learn how to resist the effect of the medicine.

Research involves gathering health information from and about human beings, as well as testing the safety and efficacy of new medicines on animals and humans. Research into disease and medicine needs to respond to human experience and has to be ongoing.

Examples: Need to overcome resistance

Consider the example of penicillin, an antibiotic derived from mould, that was used for treating bacterial infections in the 1940s. During the 1950s, almost 100% of certain types of bacterial infections could be successfully treated with penicillin. But by the 1980s, the success rate was down to less than 10%.

Another example is treatment for tuberculosis (TB). New drugs for TB have not been developed for many years, leading to more and more cases of multi-drug resistant TB.

Examples: Need for ongoing research

The vaccine for rubella (German measles) provides a good example of the need for ongoing research. In the five years after first being registered for use in 1969, the number of reported rubella cases in the United States dropped from 57 600 to 12 400. However, research had to continue once it was discovered that the efficacy of the vaccine in adults was lower than in adolescents.
Treatment for HIV/AIDS provides another. Although scientists have discovered how to use antiretroviral drugs to treat HIV infection, they have not yet discovered a cure or vaccine.

12.2 What is health research?

There are many different types of health research. The National Health Act 61 of 2003 defines “health research” as:

“any research which contributes to the knowledge of –

a) the biological, clinical, psychological or social processes in human beings;

b) improved methods for the provision of health services;

c) human pathology;

d) the causes of disease;

e) the effects of the environment on the human body;

f) the development or new application of pharmaceuticals, medicines or related substances; and

g) the development of new applications of health technology”.

Simply put, health research is not limited to the work of scientists in laboratories. Instead, it includes matters such as research on how people function socially and psychologically, as well as how health authorities may improve the provision of health care services. This chapter does not cover all aspects of health research, but instead focuses on the three most common types of health research:

- research into the safety and efficacy of medicines;
- epidemiological research; and
- operational research.

In addition, the chapter also considers the important distinction between therapeutic and non-therapeutic research, particularly important in clinical research aimed at developing new medicines and vaccines. Under the National Health Act, the rules governing research differ slightly depending on whether the research is classified as therapeutic or non-therapeutic.

Research into the safety and efficacy of medicines

Before medicines may be used, there is a long process to test whether they are safe and effective. This usually takes the form of a clinical trial, defined in section 72(7) of the National Health Act as:

“a systematic study, involving human subjects, that aims to answer specific questions about the safety or efficacy of a medicine or method of treatment.”
Research into the safety and efficacy of medicines goes through a number of stages, starting with pre-clinical (or basic science) research that is usually conducted in a scientific laboratory. Pre-clinical research focuses on microbes, chemicals and other substances, aiming to develop or find active pharmaceutical ingredients (APIs) that will be effective in the treatment and/or prevention of disease.

Once a potential chemical has been identified, it is then tested on animals. If it can be demonstrated that it is safe and effective with animals, then it is tested on humans. Testing on human volunteers is done in several phases.

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>This involves testing a medicine on a small number of healthy people, called subjects. It tests the safety of a medicine in healthy subjects and aims to ensure that it does no harm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>If a medicine passes a Phase 1 trial, it is then given to larger numbers of volunteers (up to 500). It is now being tested on subjects who have the disease or condition to be treated, or in people who are vulnerable to contracting the disease. Phase 2 trials aim to confirm safety and also to begin to examine whether the medicine works – called efficacy.</td>
</tr>
<tr>
<td>Phase 3</td>
<td>If a medicine shows promise in a Phase 2 trial, it is usually followed by a Phase 3 trial, which may involve thousands of people. Its aim is to confirm and gather data on the medicine’s efficacy. If a Phase 3 trial shows that a medicine is safe and effective, this information is usually collected and used to register the medicine for general use.</td>
</tr>
<tr>
<td>Phase 4</td>
<td>After a medicine has been registered, its use continues to be monitored in order to gather more information on larger numbers of people, or to compare the medicine’s efficacy with other medicines.</td>
</tr>
</tbody>
</table>

See Chapter 14 for more information on the development and registration of medicines.

**Epidemiological research**

*Epidemiology* is defined in the Oxford English Dictionary as “the study of the incidence and distribution of diseases and their control and prevention”. Epidemiologists collect and analyse information about population health.

Epidemiology is very important for public health programmes because it allows governments to detect new causes of disease (such as SARS) before they infect large numbers of people and the disease becomes an epidemic. Epidemiology also allows health authorities to monitor the prevalence and incidence of known causes of disease (such as TB) and death (such as maternal or child mortality).
Example: Prevalence of HIV amongst pregnant women

Every year, the DoH carries out a study to discover the prevalence of HIV infection amongst pregnant women. This means taking pregnant women’s blood samples and anonymously testing them for HIV. This type of research is called a sero-prevalence study.

Certain types of epidemiological research are ongoing. Under the National Health Act, for example, the Minister of Health has the power to pass regulations declaring certain diseases to be notifiable. This means that health professionals must report every case of that disease that they diagnose. At the moment, there are 33 notifiable medical conditions, including TB, yellow fever, malaria and measles.

**Operational research**

Research is often conducted into the working of the health system, as well as the implementation of specific health programmes. This may be to find out whether the system or the programme is working properly and what needs to be done to improve its management.

Operational research is not as physically invasive as clinical research, as it involves interviews with patients or health providers, or a review of patient medical records. It is conducted in settings where patient information is confidential, such as hospital wards or HIV counselling and testing centres. A patient must give informed consent before operational research is carried out. It must also be approved by a research ethics committee.

**Therapeutic and non-therapeutic research**

Medical research cannot be done without human volunteers. They will either be healthy people who agree to be volunteers in the public interest, or sick people who volunteer because the research may benefit them. This difference forms the basis of the distinction between therapeutic and non-therapeutic research:

- **Therapeutic research** tests medicines that may be of direct benefit to the person who is participating in the research.
- **Non-therapeutic research** involves using a trial medicine or vaccine on a healthy person for whom it may have no benefit at all. Testing a candidate medicine during Phase 1 or 2 trials obviously has some risks for the safety of a volunteer, because the effect of the medicine on their bodies is not yet understood.
The main difference between these two types of research is that the risk-benefit ratio is different. A person who is already living with cancer accepts the risks of being part of a trial, partly because that person may benefit if the medicine works. A healthy person agreeing to be part of a vaccine trial accepts a risk even though there may be no personal benefit at all.

We will explain how law and ethics have made a distinction between these two types of research. However, it is also important to be aware that in recent years important organisations like the Council for International Organisations of Medical Sciences (CIOMS) have discarded this distinction.

For example, the CIOMS 2002 International Guidelines for Biomedical Research Involving Human Subjects removed the distinction. Organisations like CIOMS argue that it is misleading to classify a trial as therapeutic when some of the participants may be receiving a placebo (a drug with no active ingredients) and therefore will get no immediate benefit from the trial.

**Testing of drugs**

Therapeutic research may involve testing a cancer drug on a person with cancer or new antiretrovirals on a person living with AIDS. In this case, the drug’s efficacy is measured by its impact on the volunteer’s health. Non-therapeutic research, on the other hand, may involve testing the safety of an AIDS vaccine on a person who does not have HIV. This is because the research is needed to understand the safety profile of a product that could cause life-threatening adverse reactions.

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### CIOMS Guideline 8: Benefits and risks of study participation

For all biomedical research involving human subjects, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimised:

- Interventions or procedures that have the prospect of direct diagnostic, therapeutic or preventive benefit for the individual subject must be justified by the expectation that they will be at least as advantageous to the individual subject as any available alternative. Risks of “beneficial” interventions or procedures must be justified in relation to expected benefits to the individual subject.

- Risks of interventions that do not have the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society (called generalisable knowledge). The risks of these interventions must be reasonable in relation to the importance of the knowledge to be gained.

Source: CIOMS website
12.3 Protecting people from harmful or abusive research

Health research may involve research on human subjects that puts them at risk. People participating in clinical trials must receive plain and easy-to-understand explanations of the many complex medical terms that researchers often use to describe the procedures of clinical trials. If this does not happen, they are not giving proper informed consent when they agree to participate in a trial.

An important ethical issue arising from the distinction between therapeutic and non-therapeutic research is the need to protect people who may not be able to give informed consent, particularly children, from being put at risk in non-therapeutic research. Even where research volunteers are able to give informed consent, they may nevertheless still be vulnerable to harm and exploitation. Sometimes the risk of harm might arise from simple things like different languages spoken by researchers and volunteers, meaning that volunteers do not fully understand the issues.

Examples: People who are vulnerable
Research volunteers or trial subjects may be:
- poor;
- sick and desperately in need of a medicine; and
- prisoners, whose confinement makes it difficult for them to protect or exercise their rights.

Conflicting interests and duties
For researchers, who are often doctors, there may sometimes be a tension between their duty of care to patients and their sense of responsibility to society as a whole, through research that aims to improve human knowledge. In theory, all medical research should be conducted in the public interest and carried out for the public good. But there may be times when what is for the “public good” may not be in the best interests of the trial participant.

There have also been times when researchers have consciously abused the human rights of research subjects. For example, although research volunteers are often poor and vulnerable, the people and institutions that carry out research may have strong self-interest or commercial interests. Because research may be very expensive and time-consuming to conduct, those who sponsor it
expect rewards for their investment, such as the exclusive right to market (and sell) the discovery.

For more on exclusive marketing rights, see Chapter 14 on patents and access to medicines. The financial and other personal rewards that can flow from research have the potential to result in the abuse of subjects. Research should therefore be monitored to make sure that researchers do not take short cuts that may endanger or exploit a research participant. This is why research ethics and law are enforced by specialist institutions such as medicines regulatory authorities that control, approve and monitor research.

Examples: Personal or financial interests
A lot of the funding for the research and development of new medicines and vaccines comes from the private pharmaceutical industry that includes some of the world’s richest and most powerful companies. A new or better medicine that benefits those who can afford it can be worth billions of dollars to the company or individual who discovers it.

But interests are not only financial:
● People who conduct research, known as principal investigators, have academic careers that are advanced by published and original research.
● Sometimes research is carried out as part of a person’s academic development, such as to achieve a postgraduate degree.

For a fictional account of the potential impact of vested interests, read John Le Carré’s novel *The Constant Gardener*, which tells the story of a powerful pharmaceutical company that tested drugs on women in Kenya without telling them and then tried to cover up their deaths.

Protection through human rights, law and ethics
Human rights, law and ethics may all be used to protect people from harmful or abusive research:
● Human rights are a universal set of standards based on the idea that all human beings are born equal with dignity and rights. But not all human rights are enforceable in law.
● Law is about the enforcement of certain rules, with the threat of penalty or punishment if these rules are not observed. For example, health researchers who ignore provisions of the National Health Act may be guilty of a criminal offence.
Ethics are about selfless internal motivation, setting guidelines that are based on morality, doing good and doing no harm. This chapter discusses how human rights, law and ethics impose different – but sometimes overlapping – duties on researchers. It also considers what happens when ethics and law seem to point in different directions.

12.4 The ethics of research on human subjects

There are many theories of and approaches to ethics. In medicine and medical research, ethics include:
- Norms or standards for guidance and evaluation of morally acceptable conduct;
- The reasons that support or oppose this behaviour; and
- The duties and responsibilities that the individual accepts and commits to as part of his or her profession.

People who work in medicine are bound by special ethical codes, such as the ancient Hippocratic Oath, in terms of which doctors pledge always to act in the best interests of their patients and to respect their privacy.

Key ethical principles for health research

Beneficence and non-maleficence

Beneficence means that a doctor must focus on acting for the good of the patient or research subject. But in health research, a researcher may experience a conflict of interest, having conflicting loyalties both to his or her patient and to science. Non-maleficence means not doing harm, such as conducting research without giving subjects the full information or protection they are entitled to.

Autonomy

The principle of autonomy means that researchers should have respect for the dignity of the people they work with. Respect for dignity means not acting in a way that insults or undermines a person’s sense of self worth. Respect for autonomy means allowing a person to take decisions without threat or undue financial incentive. It creates a duty on the researcher actively to assist the trial subject to have enough information to make a proper decision.
Justice

In the context of research, the ethical principle of justice means fairness in the selection of people involved in research and fairness in distributing the burdens and the benefits of research.

The many different challenges facing medicine and research mean that there is often a very fine line between what is ethical and unethical. This is one of the reasons why Institutional Review Board (IRB) approval is required before research can be conducted.

See page 403 for more on IRBs. For a good summary on applying these principles in research ethics, see E. J. Emmanuel, “What makes clinical research ethical?”

Example: Ethical principle of justice

It would be unethical if research were to be conducted on people in an African country for a medicine that would be available or affordable only in a European country. In such a case, the subjects involved in the trial may have exposed themselves to risk, with little possibility of benefits to themselves or their communities.

Case studies of unethical research

During the 20th century, the need to protect the ethical principles of beneficence, non-maleficence, autonomy and justice was reinforced by cases where researchers committed serious ethical violations.

CASE STUDY 1: NAZI GERMANY

In Nazi Germany during World War II, doctors carried out research on people who were detained in concentration camps. Often there was no difference between this research and torture, because it took place without consent, deliberately inflicted harm and the research had no legitimate medical purpose – except to experiment on human beings.

The research was exposed during the Nuremberg trials, which took place in 1946 after the war had ended. The Nuremberg Code was developed as an ethical standard against which to judge the research. The Code established 10 basic principles to safeguard the dignity of people involved in research, including:

- Consent to participate in research.
- Competent investigators with skill and care to conduct research; and
- Benefits to participants must be equal to the risks.

The Nuremberg Code informed the development of further ethical guidelines, including the Declaration of Helsinki – which focuses on the duties of investigators in respect of research participants – issued by the World Medical Association in 1964.
12.5 Human rights, law and health research

CASE STUDY 2: UNITED STATES

From the 1930s to the 1970s, medical researchers in the state of Alabama conducted research on the effect of syphilis on men. The trial violated the autonomy of the “volunteers” – all poor and illiterate African-American men – because they were not told about the purpose of the trial. Having no guiding protocol, the “Tuskegee study” was exposed in 1972 and led to an investigation.

The research was furthermore unethical because the researchers did not act in the best interests of their patients, who were not offered any treatment or informed about breakthroughs in the 1940s in the treatment of syphilis using penicillin. As a result of this unethical conduct, up to 100 men became ill and died.

CASE STUDY 3: PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV – CLINICAL TRIALS ON ANTIRETROVIRAL DRUGS

One of the guidelines for ethical research contained in the Declaration of Helsinki advises that when researchers are investigating new drugs, the control group of the trial should use a drug that is part of the standard of care in that country. Where there is no local standard of care, a drug with no active pharmaceutical ingredient called (called a placebo) is used.

In the late 1990s, there was a controversy about the ethics of continuing to use a placebo in clinical trials that were evaluating the efficacy of antiretroviral drugs to prevent mother-to-child transmission of HIV (PMTCT). In 1998, after a clinical trial conducted in Thailand established the efficacy of a short course of zidovudine (AZT) for PMTCT, many researchers and activists argued that it was unethical to use a placebo in new or existing trials testing other medicines for PMTCT.

It was argued that researchers were not acting in the best interests of their patients if they denied them access to a drug whose efficacy had now been established. As a result of this controversy, PMTCT trials using a placebo as a control arm were either stopped or changed.

For more on the issues raised in these case studies, see M Angell, “The Ethics of Clinical Research in the Third World” and P Lurie and SN Wolfe, “Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries”.

International law and the Constitution

Human rights are supposed to be “universal”, as they belong to all people whatever their country, religion, race, sex or any other similar ground. The Universal Declaration of Human Rights, which was approved by the United Nations General Assembly in 1948, says that all human beings are “born equal
in dignity and rights”. It also recognises the right of all people to “share in scientific advancement and its benefits”.

In 1968, the UN General Assembly adopted the International Covenant on Economic, Social and Cultural Rights (ICESCR), which affirms the right “of everyone to the highest attainable standard of physical and mental health”. Also in 1968, the same body adopted the International Covenant on Civil and Political Rights (ICCPR) that expressly states that no person “shall be subjected without his free consent to medical or scientific experimentation”. The ICCPR was ratified by South Africa in 1998.

In South Africa, human rights are recognised by and protected in the Constitution, which says that the state must “respect, protect, promote and fulfil” our human rights. The Constitution also instructs courts to consider international law when interpreting any right in the Bill of Rights.

For more about the role of international law in South Africa, see Chapter 5.

The Constitution regulates the conduct of government and the rest of society, including companies and institutions. The Bill of Rights includes rights that are relevant to research, such as rights to:

- human dignity (section 10);
- privacy (section 14); and
- access to health care, food, water and social security (section 27).

For more on the Constitution and public health policy, see Chapter 2.

The most important right to protect people from unethical or unlawful research is the right in section 12 to “freedom and security of the person”. In particular, subsection (2) of the right reads as follows:

“(2) Everyone has the right to bodily and psychological integrity, which includes the right:

a) to make decisions concerning reproduction;

b) to security in and control over their body; and

c) not to be subjected to medical or scientific experiments without their informed consent.”

Section 12 means that people have a right to control decisions that are made about their bodies and a right not to be used in research without first giving their informed consent. To date, however, no court in South Africa has explained the precise meaning of this part of the right in the context of medical or scientific research.
Laws governing health research

In addition to the Constitution, health research is also governed by a number of laws, including common law rules developed in court judgments and statutes passed by Parliament. The next section of this chapter considers some of these.

Informed consent

Informed consent is a concept that is well established both in law and ethics. In many countries, informed consent is an expression of the human right to autonomy (an integral part of the right to privacy). In South African law, there is not yet any case law on informed consent in the context of health research. But the courts have ruled that before a doctor conducts certain medical procedures and tests, informed consent must be obtained.

There are three leading cases in South African law dealing with informed consent for different types of medical treatment: *Stoffberg v Elliot* 1923 CPD 128, *Castell v De Greef* 1994 (4) SA 408 (C) and *C v Minister of Correctional Services* 1996 (4) SA 292 (T). The principles set out in these cases have largely been codified in the National Health Act 61 of 2003.

For more on the National Health Act, see pages 400 to 403 of this chapter.

Generally, informed consent is necessary where there is a risk of harm from the medical procedure. From the cases, we can argue that the legal standard of giving informed consent to participate in research is that a person must:

- agree to participate in the research (the consent); and
- understand the risks, benefits and procedures of what they are agreeing to (the informed part of the consent).

To ensure that there is real informed consent, people who are conducting research have a duty to provide a research volunteer with what the Medical Research Council (MRC) calls a “full disclosure” of all material facts of the research in a language and manner that is understandable.

The legal duty to obtain informed consent is an example of an overlap between the law and ethical responsibilities that are accepted by medical professionals. The MRC guidelines on ethics for medical research, for example, provide as follows:

“*Investigators have the duty to empower research participants, or persons giving proxy consent, to decide on participation. This includes disclosure of potential risks and benefits (or the absence of any direct benefit) and alternative treatment in the case of therapeutic research.*”
Even people who receive good counselling and information about their participation in a clinical trial may have or develop what is called a therapeutic misconception. This means that research participants start to believe that a trial drug or vaccine will definitely benefit them. Thus, for example, persons participating in HIV vaccine trials may stop using condoms because they believe that they are protected from HIV infection.

National Health Act

The primary purpose of the National Health Act (NHA), which was passed by Parliament in and assented to on 18 July 2004, but came into effect only on 2 May 2005, is to “provide a framework for a structured uniform health system within the Republic, taking into account the obligations imposed by the Constitution and other laws on the national, provincial and local governments”.

INFORMED CONSENT TO PARTICIPATE IN AN HIV VACCINE TRIAL

A vaccine trial is non-therapeutic research. If you agree to participate in a trial for an HIV vaccine, you should understand what a vaccine is, and what it is not.
The researchers have a duty to explain to you:
- A vaccine is not a cure or a treatment.
- If you receive the vaccine, you can still be infected with HIV during the trial if you do not have safer sex.
- How long the trial will last for.
- What rights to care and treatment you will have if you are infected with HIV during the trial.
- What risks you may experience as a result of the trial, such as possible discrimination if the vaccine causes you to test HIV-positive.
- Whether you or the community you come from will benefit if the vaccine is shown to be effective.
- You have the right to withdraw from the trial at any time.

INFORMED CONSENT TO PARTICIPATE IN A CLINICAL TRIAL OF A MEDICINE

Clinical trials are usually therapeutic research.
If you agree to participate in a clinical trial, you should understand:
- The medicine may not work.
- You may be part of the control group of the research (and given a placebo or a medicine that is already part of the local standard of care).
- The risk of side effects from the medicine.
- How long you will be given the trial medicine.
- What rights you have to care and treatment if you become more ill during the trial.
- Whether you will benefit personally if the medicine is shown to be effective.
The NHA is covered in detail in chapter 2 of this handbook. This chapter focuses on those parts of the law that directly address issues related to health research. One effect of the NHA’s provision on health research is to turn into law a number of ethical principles for research, particularly in relation to children. This is another example of how ethics influences and impacts on law.

CHAPTER 8: USE OF HUMAN TISSUE

Chapter 8 of the NHA, which sets out rules regarding the use of human blood, blood products, tissue and reproductive cells (“human tissues”), replaces the Human Tissues Act, 65 of 1993. It applies to research conducted on human tissues taken from people who are still living as well as from bodies after death. Consent of the donor, whether written or oral, must be given for this type of research.

In addition to the requirement of consent, chapter 8 of the NHA provides for further protections. In terms of section 68, the Minister is empowered to draft regulations about how this research should be conducted. Further, section 56 says that tissue may not be removed “which is not replaceable by natural processes from a person younger than 18 years”. Together with other provisions of chapter 8, it protects certain vulnerable groups of people – who may not be able to give proper consent – from exploitation.

CHAPTER 9: HEALTH RESEARCH AND INFORMATION

Chapter 9 of the NHA establishes two new statutory research bodies: the National Health Research Committee (NHRC) and the National Health Research Ethics Council (NHREC), both of which report to the Minister of Health. While this part of the NHA has been justifiably criticised for centralising decisions about publicly funded research with the Minister of Health, rather than allowing these – and other statutory bodies such as the Medical Research Council (MRC) – to determine their own agendas, it is nevertheless a significant breakthrough. Importantly, section 69 of the NHA aims to ensure that health research carried out by the state or its research institutions is better planned, co-ordinated and relevant to the “priority health problems” of people in South Africa.

According to the NHA, the NHREC must:
- determine guidelines for the functioning of research ethics committees;
- register and audit health research ethics committees;
- set norms and standards for conducting research on humans and animals, including norms and standards for conducting clinical trials;
- adjudicate complaints about the functioning of health research ethics
committees and hear complaints by researchers who believe that a health research ethics committee has discriminated against them;

- refer to the relevant statutory health professional council cases involving the violation or potential violation of an ethical or professional rule by a health care provider;

- institute disciplinary action as may be prescribed against any person found to be in violation of any norms, standards or guidelines set for conducting research under the NHA; and

- advise the national department and provincial departments on any ethical issues to do with research.

One of the NHRC’s key functions is to advise the Minister of Health on the country’s “health research priorities”. In so doing, the NHA requires the committee to consider:

- “the burden of disease” – whether a disease affects a large or small part of the population;

- “the cost-effectiveness of interventions aimed at reducing the burden of disease” – whether the intervention that is being researched will be affordable or will save the state money by preventing costly illnesses;

- “the availability of human and institutional resources for the implementation of an intervention at the level closest to the affected communities” – whether, if the research is successful, it will be implementable;

- “the health needs of vulnerable groups such as women, older persons, children and people with disabilities”; and

- “the health needs of communities”.

Example: Research ethics committees

The University of the Witwatersrand has a Committee for Research into Human Subjects that meets every month. Any medical research conducted by the University has to be approved by this Committee. With clinical research, the approval of this committee is necessary before an application is submitted to the Medicines Control Council (MCC).

For more on the role of the MCC, see page 409 below.

In 2006 there were 26 ethics committees operating in South Africa. The most important ones are listed below.
Higher education institutions:
University of Pretoria
University of Limpopo (incorporating the former MEDUNSA)
University of KwaZulu-Natal (formerly University of Natal)
University of Cape Town
University of the Free State
University of the North West (formerly Potchefstroom University)
University of the Western Cape
Rhodes University
Nelson Mandela Metropolitan University (formerly University of Port Elizabeth)
Cape Peninsula University of Technology (formerly Peninsula Technikon)
Durban University of Technology (formerly Technikon Natal)
Tshwane University of Technology (formerly Technikon Pretoria)
University of Johannesburg (incorporating the former Technikon Witwatersrand)

Private/professional associations:
South African Medical Association
Pharma-Ethics
AngloGold Health Service Medical Research Ethics Committee
Democratic Nursing Association of South Africa (DENOSA)

Mental Health Care Act
There are many types of mental illness, some more serious than others. Some are so serious that they leave people without the mental capacity to take legal decisions. According to the Mental Health Care Act, 17 of 2002, a person who has been declared “incapable of making informed decisions” is known as an “assisted mental care user”. When a person has been declared an assisted mental care user, his or her spouse, nearest relative or the state is granted legal authority to conduct his or her affairs. This also covers participation in medical research.

As research into mental illnesses and their treatment is important, neither the NHA nor the Mental Health Care Act specifically prohibits people with mental illnesses from participating in research. Instead, recognising that assisted mental care users are vulnerable to unethical research (there are cases in the history of medicine where people with mental illnesses have been
abused), the Mental Health Care Act says that only decisions that are “in the best interests of the mental health user” (section 7), who has the right to “respect, human dignity and privacy” (section 8) must be taken. In addition, people providing mental health services must ensure that “users are protected from exploitation, abuse and any degrading treatment” (section 11).

Other common law rules

In addition to the now-codified rules of informed consent, there are other provisions of the common law that also have an impact on health research. For example, the common law rules of contract are usually applicable to the duties of researchers regarding their duty of care. In particular, the Medical Research Council (MRC) recommends that when people agree to be volunteers in therapeutic or non-therapeutic research, they should sign a contract to show that they have given their informed consent. Such contracts ordinarily include clauses permitting the consent to be withdrawn at any time.

In addition, such contracts may also impose clear legal duties on researchers as well as the institutions sponsoring the research, known as “duties of care” – to ensure that the trial participant gives informed consent, that the trial is conducted as safely as possible and that if any person is harmed in the trial, he or she will have access to proper care and remedial treatment. If any of the ordinary common law rules or these contractual duties are violated, a clinical trial volunteer may be able to sue the researchers, bringing a delictual claim for damages.

12.6 Special issues with research on children

Children are generally more at risk of illness because their immune systems are still developing. Every year in South Africa, thousands of children die soon after birth or before they reach the age of five – in many cases as a result of mother-to-child transmission of HIV (MTCT). For these reasons, scientists need to research the causes and patterns of disease in children, just as they do with adults. But the smaller physical sizes of children – as well as their immature organs – also means that children may need different doses of medicines and that medicines that are safe for adults may be too toxic for children.

As in many other countries, South African law imposes a duty on the state to protect children from harm. When considering health research involving
children, we must remember that the Constitution states that a “child’s best interests are of paramount importance in every matter concerning the child.” This may mean, for example, that health research involving children that does not have any direct benefits for children – or may indeed harm children – should not be conducted.

**Capacity of children to contract**

We have described why the informed consent of a volunteer is an ethical and legal duty for researchers. However, the law in South Africa (and most other countries) treats children as minors – it does not allow them to enter into contracts by themselves. According to the Constitution, a child is “a person under the age of 18 years”. But some legislation, such as the Age of Majority Act, 57 of 1972, regards a child as person under the age of 21.

In addition, the age at which children are allowed to make decisions on their own differs between different laws:

- In terms of the Sexual Offences Act, 23 of 1957, children can consent to sexual intercourse from the age of 16 (19 for lesbian or gay sex).
- The Choice on Termination of Pregnancy Act, 92 of 1996 allows for a girl of any age to consent to an abortion as long as she has been properly counselled and has the mental capacity to consent.

In 2005 Parliament passed the Children’s Act, 38 of 2005. Although this Act has not yet been brought into force it has a number of important provisions which will be relevant to medical research in relation to children. For example, as a general rule it lowers the age at which children can consent on their own to medical treatment to over 12 (it is presently 14) as long as “the child is of sufficient maturity and has the mental capacity to understand the benefits, risks, social and other implications of treatment” (section 129). Presumably, this would also apply to a child’s participation in medical research.

In addition to this the Children’s Act stresses that children have a right to information on all aspects of health care (section 13); to participate “in an appropriate way” in any matter concerning that child and to have his or her views “be given due consideration” (section 10); and always to have the best interests standard applied in all matters concerning care and well-being, including health care (section 9).

Specifically the Act says that children with chronic illnesses have the right “not to be subjected to medical ... practices that are detrimental to [their] health or wellbeing” (section 11).
As pointed out above, this Act is expected to become law only in 2007 or 2008. However, it brings some legal clarity to issues concerning research into child health. This is reinforced by the provisions of the National Health Act. See Chapter 9 for more about health law and policy regarding children.

Consent of the Minister of Health

The NHA makes a specific distinction between therapeutic and non-therapeutic research on children. In respect of the latter, section 71 says that even if a parent or legal guardian consents, the research may take place only “in such a manner and on such conditions as may be prescribed” and with “the consent of the Minister.” In particular, section 71(3)(b) forbids the Minister from giving his or her consent for research on children if:

- “the objects of the research or experimentation can also be achieved if it is conducted on an adult”; or
- “the research or experimentation is not likely to significantly improve scientific understanding of the minor’s condition, disease or disorder to such an extent that it will result in significant benefit to the minor or other minors”.

Unfortunately the meaning of these provisions is open to interpretation, particularly because key words (including “minor”, “therapeutic purpose” and “significant benefit”) have not been defined in the Act.

Ethical issues with children

Even if medical research on children is conducted with legal consent, health professionals will still want to consider ethical issues that arise. Regardless of whether a particular child is able to give his or her legal consent, efforts must be made to obtain the informed consent of the child if he or she is mature enough to understand and take an autonomous decision on participation in the research.

It is possible that the law and ethics may conflict. If the child says “no”, even though the parents have consented, ethics would require the researchers to respect the child’s decision. Even if the child says “yes”, researchers’ ethical duties may remain, given that children are more vulnerable to harm. For example, children may not fully understand the research – even if it is fully explained to them. In addition, children and adolescents may be more likely to have therapeutic misconceptions.
12.7 Statutory institutions and policies governing health research

There are a number of government institutions and statutory bodies responsible for approving, regulating, monitoring and carrying out health research, including the following:

- National Department of Health;
- Medicines Control Council (MCC);
- Medical Research Council (MRC);
- Health Professions Council of South Africa (HPCSA); and
- Human Sciences Research Council (HSRC).

**National Department of Health**

The National Department of Health (NDoH) falls under the responsibility of the Minister of Health and the Director-General of Health, with the Constitution and the NHA governing its activities.

In particular, the Minister has overall responsibility for public health research, and is advised by the National Health Research Committee (NHRC) and the National Health Research Ethics Committee (NHREC). The NHRC has up to 15 members who are appointed by the Minister after consultation with the National Health Council. The NHREC also has 15 members and is also appointed by the Minister. Both committees will come into operation in 2007.

**CASE STUDY: HIV VACCINE TRIALS ON CHILDREN AND ADOLESCENTS**

Phase 1 HIV vaccine trials were launched in South Africa in 2003. Only adult volunteers were selected because at this stage only the safety of the candidate vaccines is being evaluated. However, phase 2 and 3 trials will need larger numbers of volunteers, including adolescents and children. This is necessary because an HIV vaccine is designed to protect people from sexually transmitted HIV infection and many infections in South Africa occur among young people.

While a vaccine trial is non-therapeutic research, a candidate vaccine in phase 2 and 3 trials is likely to pose little or no safety risk. But there is a risk that children or adolescents on these trials may experience harm because of the stress of repeated HIV tests, therapeutic misconception or discrimination. According to the NHA, the Minister will have to consent to children's participation in vaccine trials. Even if she agrees and issues ethical guidelines, researchers will still have to obtain informed consent from the children and their parents.
To date, the NDoH has published a range of guidelines that, although based on internationally accepted ethical and legal principles, are not directly enforceable. However, the conduct of those who act in a way that is contrary to the guidelines should be reported to the relevant authorities. In addition, the guidelines may assist courts in interpreting laws and provisions of the Constitution that apply to health research.

**INTERNATIONAL GUIDELINES**

- World Medical Association, Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects (1964).
- UNAIDS Guidance document, Ethical Considerations in HIV Preventative Research (May 2000).

The NDoH’s guidelines that are relevant to health research include the following:

- **Code for Good Clinical Practice** (undergoing review).
- **Guidelines for Good Practice in the Conduct of Clinical Trials in South Africa** (2000);
- Ministerial Committee on Health Research Ethics: *What you Should Know When Deciding to Take Part in a Clinical Trial as a Research Participant* (December 2002);
- **Ethical Considerations for HIV/AIDS and Epidemiological Research** (2000); and

**Medicines Control Council**

Established by the Medicines and Related Substances Control Act 101 of 1965 (the Medicines Act), the Medicines Control Council (MCC) is responsible for the approval and monitoring of all clinical trials in South Africa, whether conducted by public or private bodies. The MCC’s Clinical Trials Committee, which meets every six weeks, considers applications to conduct trials.

Section 35 of the Medicines Act empowers the Minister, in consultation with the MCC, to make regulations “relating to the control and conduct of clinical trials”. Among other things, these regulations say that all applications
for clinical trials must include “[a]n informed consent document and endorsement by any ethics committee recognised by the Council.”

For the overall role and responsibility of the MCC, see Chapter 14.

The MRC’s Guidelines on Ethics for Medical Research (paragraphs 9.5-9.12) give a comprehensive guide to the duties of research ethics committees. The MRC describes their aims as being to:

- maintain ethical standards of practice in research;
- protect research participants and investigators from harm or exploitation;
- preserve the research participant’s rights, as these take preference over society’s rights; and
- provide reassurance to society that these aims are being carried out.

The MCC’s Regulations on the Conduct of Clinical Trials for Humans say that even after the MCC has authorised a trial, it may still “request additional information, inspect a clinical trial or withdraw the authorisation … if the council is of the opinion that the safety of the subjects of the trial is compromised, or that the scientific reasons for conducting the trial have changed”. People who are concerned about the conduct of clinical trials should be aware of these powers and report misconduct to the MCC.

**Other MCC Guidelines and regulations**

- Regulations on the Conduct of Clinical Trials for Humans (2003).

**Medical Research Council**

The purpose of the Medical Research Council (MRC) is to use research to “promote the improvement of health and quality of life” of people in South Africa. Set up by an Act of Parliament and funded from the national budget, the MRC is nevertheless governed by an independent board. It is empowered to decide independently on the nature of the research it conducts, but can also carry out research for the government or any other person. Under the empowering statute, the MRC’s board is allowed to “determine ethical directives” for research and to “take measures … to ensure that the ethical directives are complied with.”
In the past, the MRC had a duty to advise the Minister of Health on policy and priorities regarding research, as well as on the development, promotion, implementation and co-ordination of research on a national basis. However, this role is now likely to be taken over by the NHRC.
For more on the NHRC, see page 401.

**MRC GUIDELINES**
- Book 1: Guidelines on Ethics for Medical Research: General Principles
- Book 2: Guidelines on Ethics for Medical Research: Reproductive Biology and Genetic Research
- Book 3: Guidelines on Ethics for Medical Research: Use of Animals in Research
- Book 4: Guidelines on Ethics for Medical Research: Use of Biohazards and Radiation
- Book 5: Guidelines on Ethics for Medical Research: HIV Vaccine Trials

**Health Professions Council of South Africa**
Under the Health Professions Act 56 of 1974, all doctors, dentists and psychologists must be registered with a statutory body known as the Health Professions Council of South Africa (HPCSA).

Section 15 of the Health Professions Act allows the HPCSA to establish professional boards, whose tasks include:
- assisting in the promotion of health;
- maintaining and enhancing the “dignity of the profession and the integrity of” health professionals.
- guiding “the profession to protect the public”.

The HPCSA has a Medical and Dental Professions Board that has published a number of Guidelines on Research. It also has an Ethics and Human Rights Committee that advises the Board.

**HPCSA GUIDELINES**
- Medical and Dental Professions Board, General Ethical Guidelines for Health Researchers, Booklet 2
- Medical and Dental Professions Board, Guidelines on Research and Clinical Trials Involving Human Subjects: Ethical Principles, Booklet 9
Human Sciences Research Council

The Human Sciences Research Council (HSRC) falls under the Ministry of Education. It is tasked with research into “human sciences” – these are defined as “sciences concerned with the study of creations and the manner of mental activity of man, human development, or mutual relationships, institutions or conditions in society”.

Although the HSRC does not carry out clinical research, it does undertake research into patterns of behaviour, knowledge and understanding that impact on health. In recent years, for example, the HSRC has collaborated with the MRC and other organisations on a number of studies of HIV prevalence and risk behaviour, including the 2002 and 2005 *South African National HIV Prevalence, Behavioural Risk and Mass Media Household Survey*. Ethics and laws also govern this type of research.


12.8 Conclusion

The aim of this chapter has been to provide an introduction to the laws, policies and ethics that guide research into health. This is a complex field, with many ongoing controversies and disputes. Readers are encouraged to look at the *References and Resources* section of this book as a guide to further reading.

Research into health has the potential to bring about great good for society if it is done properly – as well as harm to individuals if it is done badly. These are the reasons that it is important for all health users to understand and take an active interest in health research.

Finally, it is important that health research is actively encouraged and supported by the government. In particular, it is essential that developing countries such as South Africa establish a research agenda into health that is based on our health needs – and not those of rich countries where health priorities and disease are often very different.