



GUIDELINES ON ETHICS FOR MEDICAL RESEARCH: **GENERAL PRINCIPLES**

INCLUDING

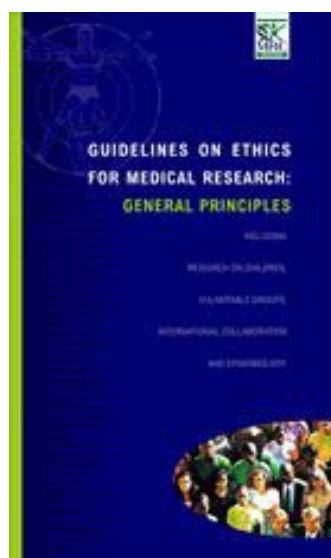
RESEARCH ON CHILDREN,

VULNERABLE GROUPS,

INTERNATIONAL COLLABORATION

AND EPIDEMIOLOGY.





Book 1: General Principles including research on children, vulnerable groups, international collaboration and epidemiology.

Preface

Foreword to the fourth edition

1 What is the South African Medical Research Council's ethics policy?

- 1.1 General policy
- 1.2 For whom are these Guidelines intended?
- 1.3 Ethics principles
- 1.4 Conclusion

2 What is research?

- 2.1 What constitutes research on humans?

3 What is meant by research ethics?

- 3.1 General philosophical concerns and human or anthropological perspectives on ethics in medical research

4 The medical justification for research

- 4.1 Healthy volunteers
- 4.2 Patients

5 The legal and moral justification for research

- 5.1 Consent is essential
- 5.2 Form of consent
- 5.3 Requisites of consent
- 5.4 Participant's friend

6 Conduct of research

- 6.1 Responsibility for overall care of patients
- 6.2 Responsibility in the conduct of multicentre studies
- 6.3 Delegation and research conducted by non-medical healthworkers
- 6.4 Responsibility for the welfare of research workers and laboratory personnel
- 6.5 Adequacy of facilities to carry out research
- 6.6 Participant privacy and confidentiality

7 Research principles

- 7.1 Research on healthy volunteers
- 7.2 Research on patients

8 Ethics issues in qualitative research

- 8.1 Introduction
- 8.2 Practical ethics issues in qualitative research

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9 Assessment of the ethics of research

- 9.1 Independent ethical review
- 9.2 Knowledge of involvement
- 9.3 Clinician-patient relationship
- 9.4 Role and competence of the investigator
- 9.5 Research Ethics Committees
- 9.6 Objectives
- 9.7 Scientific misconduct
- 9.8 Function of Research Ethics Committees
- 9.9 Membership of the Committee
- 9.10 Method of working
- 9.11 Suggested format for applications to Research Ethics Committees
- 9.12 Assessing the value and risks of research
- 9.13 Financial transactions and inducements

10 Monitoring the conduct of research

- 10.1 National ethics body
- 10.2 Particular role of the Research Ethics Committee
- 10.3 Research in progress
- 10.4 Ownership of results of research
- 10.5 Research results
- 10.6 Legal implications and arrangements for compensation
- 10.7 Publication and authorship
- 10.8 Liaison with the public media

11 International collaborative research

- 11.1 Concerns
- 11.2 Ethics principles
- 11.3 Collaborators
- 11.4 Principles

12 Ethics guidelines for epidemiology

- 12.1 'Public' versus 'health'

13 References

Recommended websites for more information

14 Appendices

Appendix I: MRC checklist: **quantitative research**

Appendix II: MRC checklist: **qualitative research**

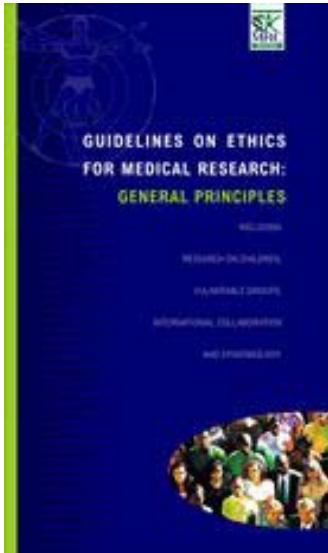
Appendix III: **Sample information sheet**

Appendix IV: **Clinical trial compensation guidelines**

Appendix V: **The Belmont Report**

Appendix VI: **Declaration of Helsinki**

Appendix VII: **The Nuremberg Code**



Book 1: Preface

The Medical Research Council of South Africa has a 33-year experience and history of ethics in health sciences research. The entrenchment of the culture of human rights as core value in health research and as one of the four strategic goals of the MRC, has elevated the critical role ethics play in the conduct of research and in society-particularly in a developing country undergoing major changes. Ethics is an integral part of every research project but, more critically, ethics is vital for improving the quality of research.

The 1st (1977) and 2nd (1987) editions of the MRC guidelines on ethics outlined general philosophical approaches to research ethics based on the Declarations of Helsinki and Nuremburg which, while brief, had to be read.

The 3rd (1993) edition differed considerably from the first two by presenting information in a codified form with more detailed, specific recommendations. It was more of a handbook than the first two editions and could be used as a ready reference. Under the Chairmanship of Professor Solomon Benatar and his co-authors, this was an excellent handbook.

The 3rd edition was closely based on guidelines of the Royal College of Physicians of London with some flavour for South Africa, but the thrust was essentially that of a developed country - which reflected world-wide trends at the time and also fitted the concepts put forward by WHO and CIOMS. Of the four principles of ethics (autonomy, beneficence, non-maleficence, justice), non-maleficence was emphasised - a somewhat traditional and paternalistic approach. The guidelines were nevertheless very useful for South African researchers and have been used as the 'gold' standard by South African research ethics committees.

A number of important factors necessitated the revision of the MRC ethics guidelines:

- i. major sociopolitical transformation in South Africa since 1993 plus the South African Constitution with its Bill of Rights;
- ii. the Truth and Reconciliation Commission; and
- iii. a surge of interest world-wide in the field of bioethics, particularly as transgressions of ethics around the world have been exposed.
- iv. In addition to these factors, two major scientific events - the revolution in biology often referred to as the Human Genome Project, and the HIV/AIDS epidemic that is sweeping sub-Saharan Africa - have elevated ethics, raising issues such as the following:
 - o Will genetic coding, embryo stem cell research, the cloning of Dolly by Scottish researchers, the current human cloning debates, and germ-line therapy redefine how illnesses are treated?
 - o Will the HIV/AIDS epidemic define the African Renaissance in terms of ethics, morality and innovations? Will the current unequal access to anti-retrovirals,

the 'virodene' saga, the availability and accessibility of anti-retroviral therapy for mother-to-child transmission of the human immunodeficiency virus and in the public health systems, and the impending availability of HIV vaccine candidate products for clinical trials mainly in developing countries, raise imponderable ethical questions for researchers in society?

- v. In addition, in the past few years research ethics guidelines have been reviewed and published elsewhere, for example in Australia and Canada, the latter being a co-operative effort between three research councils. While maintaining established general principles, each increased their local flavour. There has also been a rise in awareness that developing countries have situations different to developed countries and that individuals and communities in these countries have the right not to be exploited.

So, for the 4th edition the MRC Ethics Committee decided that the guidelines must have emphasis on South African needs, and that the dignity of the individual (autonomy) and the importance of informed consent would be strongly emphasised, particularly since informed consent is entrenched in our Constitution's Bill of Rights.

The MRC Ethics Committee wanted to cut down on duplication of sections within the 3rd edition and other international and SA guidelines, hence the removal of clinical trial guidelines from the MRC book in favour of the International Conference on Harmonisation and South African National Department of Health clinical trial guidelines. There was no reason to 'reinvent the wheel'.

The revised guidelines have tried to ensure that the concept of 'the best interest of the research participant' is clear. We have changed the term 'research subject' to 'research participant' to emphasise that research is a partnership; and changed 'doctor' to 'clinician' to make it clear that clinical research is not done only by doctors.

These guidelines emphasise that developing communities must not be exploited and that in some way participating communities must benefit from the research done in or with them.

The MRC Ethics Committee decided on a number of booklets instead of one tome to allow easy updating because research ethics is a 'fluid' field constantly changing. Contributors to each book were chosen for their knowledge and expertise in specific fields. So, while the series editors oversee the production of the books, each book has its own contributors. In this way many colleagues from a variety of disciplines across the country have been involved, which we hope will increase a sense of ownership, multiple perspectives and interpretations. Each book draft was placed on the MRC web site for comment, to widen awareness of the rewriting.

The challenges facing health science research and its development are no longer technical but largely social. The future of health science research lies in the three areas of ethics, communication and attending to societal concerns. The need for science to be understood by the public; the need for scientists to communicate better; the need for the public to make choices about what science has to offer in their daily life; the need for the public to participate in and shape the scientific process; and the need for science to integrate the wealth of information that is already existent (convergence theory) have never been greater than today. These are the ideas or questions that are exercising the minds of ethicists, policy planners, health educators, academic researchers and societies that take long-term strategic planning seriously and as part and parcel of innovation and international competitiveness.

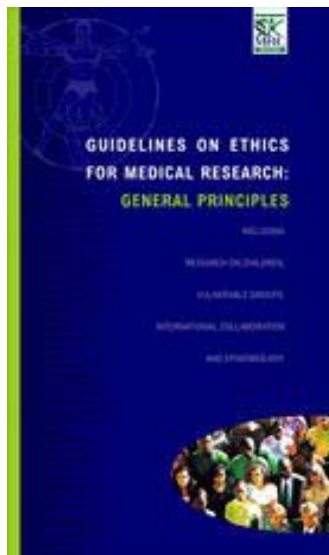
In conclusion:

- i. Ethics of research in a developing country poses exciting challenges for scholars, practitioners and communities that are driven by the principles of equity, human rights and the genuine protection of both the powerful and powerless.
- ii. Ethics in developing countries continues to demystify and destroy the male liberal racial theory that emerged in the last century.
- iii. Informed consent that is based on the language, idiom and culture of the participant is empowering, not only to the subject but also to the investigator.
- iv. Ethics in developing countries remains an important beacon of hope, an integral component and an instrument of transforming society, consolidating young democracies, defining national identities, reclaiming lost cultures and contributing to the global village.
- v. Ethics allows us to probe and understand the intricate, multifaceted nature of and subtle relationship between power and equality.

These guidelines are the first step in trying to provide information and answers to some of these challenges and dilemmas.

On behalf of the MRC, I want to thank Professor Peter Cleaton-Jones and his Committee and all those who have taken their time to participate and contribute to the development of these guidelines. Many researchers and participants will use this set of updated guidelines to the benefit of society and the improvement of health research.

Dr Malegapuru Makgoba
MRC President



Book 1: Foreword to the fourth edition

In his foreword to the third edition of these Guidelines, Professor Solly Benatar eloquently wrote of the 'resurgence of interest in the moral aspects of medical practice' including research. In the intervening years, that interest has increased at an exponential rate. Investigators, participants and sponsors have become more aware of rights and responsibilities.

This increase in ethics information has made the task of the Editorial Committee a difficult one. We decided to keep the basic framework of the third edition, but to split the original single volume into five. Our reasoning is that this will facilitate future updating and reprinting and will enable people with specific interests to find the book that suits them best. We tackled much of the task ourselves, but approached experts in specific fields to produce specialised sections. To these colleagues we are indebted, and they are acknowledged in the front of each book. Draft copies were placed on the South African HealthInfo website (<http://www.sahealthinfo.org/ethics/ethics.htm>) for comment, and we thank those people who responded.

As with anything written by different teams, there are differences in style for which we ask our readers' indulgence. Fortunately the differences have been eased by the editorial skills of Mr Brian Johnson-Barker. For consistency throughout the books, the 'research subject' has been replaced with 'research participant' to emphasise the team approach, 'researcher' is now 'investigator' and 'doctor' is now 'clinician'. This last term acknowledges that clinicians other than doctors do medical research.

The large section on clinical trials that appeared in the third edition has been removed. In its place there is reference to South African and international Good Clinical Practice Guidelines. We saw no need to reinvent the wheel and thereby waste scarce resources.

Of course these Guidelines are among many produced round the world. While all share principles, inevitably there are differences. Such differences have been starkly indicated by the passionate response to the 2000 revision of the Declaration of Helsinki (Appendix VI) which has been welcomed by some and rejected by others. Our Guidelines have a developing-country perspective, an African outlook, we believe. Our approach has been strongly influenced by the South African Constitution, which was adopted in 1996 and entrenches in the Bill of Rights the principle of informed consent of participants in medical and scientific experimentation. Given the vulnerable populations in our country, the Editorial Committee's decision has been to emphasise the principle of autonomy - particularly from the perspective of 'non-exploitation' of research participants. The theme of 'informed consent' recurs throughout. This is a complex matter and recommended reading includes the excellent compendium of views produced by the British Medical Journal (Doyal L, Tobias JT, Editors. Informed consent in medical research. London: BMJ Books, 2001: 1- 334).

There are two final points. First, there is considerably more 'legalese' in this edition. This is deliberate and has arisen from the many queries directed to members of the Ethics Committee. Second, we accept that there will be colleagues who disagree with some things we have written; some may have additional points and some may spot errors. Please send comments to the MRC (see the HealthInfo website mentioned opposite) so that whoever writes future editions may consider them.

The Editorial Committee

There are five books in the series Guidelines on Ethics for Medical Research.

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

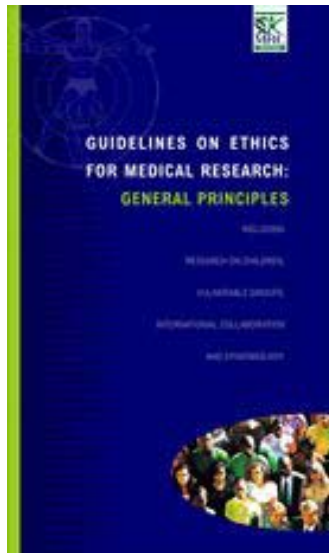
Guidelines on Ethics for Medical Research: Use of Animals in Research.

Book 4

Guidelines on Ethics for Medical Research: Use of Biohazards and Radiation.

Book 5

Guidelines on Ethics for Medical Research: HIV Vaccine Trials.



1. What is the South African Medical Research Council's ethics policy?

1.1 General policy

The MRC recognises injustices in our past and subscribes to the values enshrined in the Constitution of the Republic of South Africa Act, No 108 of 1996: human dignity, the achievement of equality and the advancement of human rights and freedoms.

The ethics policy of the MRC is clear. All research sponsored by the Council must be of the highest ethics standard. No research will be sponsored without ethics clearance from a Research Ethics Committee recognised by the Council and operating in accordance with MRC ethics guidelines.

1.2 For whom are these Guidelines intended?

The MRC Guidelines are concerned with research on human participants and animals. The Guidelines consider all forms of research on individual persons, whether they be volunteers or patients, and include the study of treatment which might benefit the individual patient (therapeutic research) and the acquisition of knowledge that may be of no immediate benefit to the healthy volunteer (non-therapeutic research). These Guidelines apply also to non-clinical research on humans. Guidelines on ethics in the use of animals in research are dealt with in Book 3 of the current MRC Guidelines series.

What follows in the chapters of this Book 1 of the series ***Guidelines on Ethics for Medical Research*** is extensively based on three previous editions and on international documents 1-9 (see also Appendices V - VII) but is adapted for South African conditions and law.

1.3 Ethics principles

1.3.1 The MRC promotes the four principles of biomedical ethics:

- autonomy (respect for the person - a notion of human dignity)
- beneficence (benefit to the research participant)
- non-maleficence (absence of harm to the research participant)
- justice (notably distributive justice - equal distribution of risks and benefits between communities)

There is considerable debate about whether one or more of these principles require or deserve preference when ethical problems are considered. For example, the trend in most Western countries seems to emphasise autonomy over beneficence. This counters the alleged danger of paternalism in the practice of medicine, and emphasises the importance of the consent and freedom of patients in making decisions about their own health and well-being. Such views are questioned in the context of many developing countries, where

solidarity within communities is valued together with respect for individual choices, and where there is increasing concern about conflict between personal autonomy and public safety in the face of, for example, infectious diseases such as tuberculosis and, particularly today, the HIV/AIDS pandemic. Concern for distributive justice in developing countries also enjoys a higher priority than in some wealthy Western nations.

The MRC is convinced of the importance of adherence to the four classical principles of biomedical ethics, and of the importance of human rights and individual dignity, but it takes no prejudicial position in debates on the ranking of these principles. The MRC also does not commit to any one approach to moral reasoning or to any one strategy for the resolution of complex ethical dilemmas. It seems clear that, in most disputes in biomedical ethics, some balance between the four principles should be pursued. In maintaining commitment to the classical principles, the complexities of each case must be understood and taken into account in any effort to make justified moral judgements. Of more importance than the consistent adherence to a specific approach or strategy for the resolution of moral dilemmas, is the willingness and ability to justify whatever position is taken, through sound moral reasoning.

1.4 Conclusion

Application of ethics standards requires a critical evaluation of the relative merits of each of the four principles of ethics to produce a harmony appropriate to a particular research project.

2. What is research?

2.1 What constitutes research on humans?

2.1.1 Clinical practice

When an activity is undertaken with the sole intention of benefiting an individual patient, and where there is a reasonable chance of success, that activity may be considered to be part of clinical practice. The progressive modification of methods of investigation and treatment, in the light of a clinician's experience, is a normal feature of clinical practice and should not be considered as research.

2.1.2 Research

Research is a systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalisable knowledge. Any such investigation raises ethical issues. The issues themselves may be small, but because studies may involve subordination of at least the immediate interest of the individual participant to the objective of the advancement of knowledge, they must be subject to ethics review.

2.1.2.1 Therapeutic research

The aim of therapeutic research is to benefit the individual research participant or patient by treating or curing their condition.

2.1.2.2 Non-therapeutic research

The aim of non-therapeutic research is to benefit people other than the research participant. The participant or healthy volunteer may unexpectedly become a direct or indirect beneficiary of non-therapeutic research. The acquisition of knowledge may be of no immediate benefit to the participant or healthy volunteer.

2.1.2.3 Intervention research

This is always invasive and interferes with the research participant's mental or physical integrity by, for example, the removal of bodily material, the introduction of (contrast) fluids into the body or the use of a procedure or method that has not been adequately tested. It

always involves risks, the magnitude of which may be unpredictable.

2.1.2.4 Observation research may be:

- i. non-invasive, involving no risk and no interference with the mental or physical integrity of the human being; for example, the unlinked and anonymous gathering of information about the person by means of a questionnaire or from clinical records, the unlinked and anonymous examination of a specimen taken from a patient for a clinically indicated intervention; measuring; observing.
- ii. invasive of mental or physical integrity, but involving no risks or only negligible risks which are known from routine medical experience; for example, the taking of one blood sample, the collection of urine or of slightly more bodily material than is strictly necessary for a normal, medically indicated intervention.

2.1.3 Clinical practice and research

The distinction between clinical practice and research is often less clear than is suggested above, because both may be practised simultaneously on the same person. Any activity aimed at obtaining knowledge affecting a person in any way, and which is additional to ordinary clinical practice, is to be regarded as research (see also 7). A useful rule of thumb is that if this new knowledge is generalised or transferred to others, or presented at a scientific meeting, or submitted for publication or for a higher qualification, it is research. Clinical audits through examination of patient records; observation of activities of individuals; health systems research to improve efficiency, cost-effectiveness and equity in health care, all are recognised as valid research.

2.1.3.1 Non-clinical research

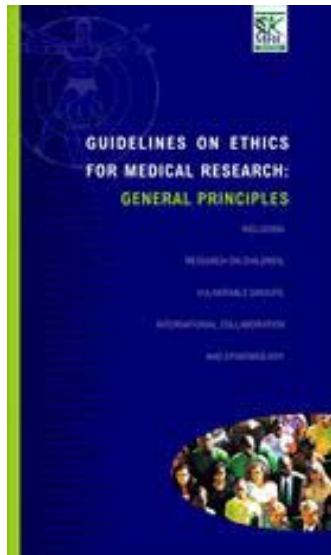
This type of research includes studies of anatomy, physiology and laboratory investigations not involving patients.

2.1.4 Innovative treatment

- 2.1.4.1** Sometimes special circumstances of an individual patient's illness lead a clinician to step outside what is accepted as normal clinical practice. Innovative treatment does not necessarily constitute research.
- 2.1.4.2** In innovative treatment, the sole motive for the action is to choose the best possible course for the individual patient, even though it may be unconventional. The responsibility for using innovative treatment is that of the clinician, who remains subject to the usual constraints that direct ordinary clinical practice.
- 2.1.4.3** Where a clinician contemplates a marked divergence from normal clinical practice in an individual case, with the prime purpose of acquiring information for application to future patients, the activity becomes research and must be subject to all the considerations of proper informed consent and scrutiny by Research Ethics Committees described here. A useful rule of thumb is to consider the 'intent' of the clinician - if the intent is to apply information to others, or to present it at a scientific meeting, or submit it for publication or for a higher qualification - in other words, to contribute to generalisable knowledge - this is research.
- 2.1.4.4** When a major innovation is called into regular use and the procedure is not yet incorporated into clinical practice generally, the innovation should become the subject of formal research without delay, so that its true worth may be established.

2.1.4.5 Quantitative research focuses on concise concepts as well as on variables, and collects information under controlled conditions. It uses structured and established procedures to collect information, and uses objectivity in the analysis of information. Quantitative research analyses numerical information using statistical procedures, it involves logistic and deductive reasoning, and the investigator does not interact with the event being researched.

2.1.4.6 Qualitative research attempts to understand phenomena in entirety. It comprises research to understand social and cultural problems, and focuses on interactive processes to collect subjective information that is not structured numerically, but intuitively. Qualitative research attempts to understand human experience. It analyses thematic and narrative information. The investigator interacts with people in a sustained manner.



3. What is meant by research ethics?

3.1 General philosophical concerns and human or anthropological perspectives on ethics in medical research

3.1.1 Medical ethics

Ethics is the science of criteria, norms and values for human action and conduct. It is engaged in reflection and analysis of morals concerning whether an act is good or bad and how it influences our basic quest for meaning, our search for humanity and our attempt to create a humane society. Its intention is to safeguard human dignity and to promote justice, equality, truth and trust. In a nutshell, ethics is critical reflection on morality.

Medical ethics is not only about the moral behaviour of clinicians, but about ethics and health care. It can be described as the reflection on moral actions within the framework of health care. Its objective is to promote health, to care, to heal, to alleviate pain and to prevent suffering.

Ethics for health research is the enterprise that determines norms and values to guide the systematic reflection and scientific evaluation or assessment of clinical knowledge and any form of experimentation or survey, with the prime objective of promoting health care. Its sole intent is to benefit patients, to alleviate pain and to prevent suffering.

3.1.2 Basic assumption and point of view

The basic ethical assumption in health research is the autonomy of the individual within the broader context of human relations. The social and cultural environment should be taken into consideration in all circumstances. People should be treated as human beings in the context of their social, political, economic and religious environments. Assessment of both patients and healthy volunteers in research programmes should be made within the context of the family and cultural system. Research programmes should treat people as part of a community while simultaneously respecting their individual autonomy. This is of paramount importance for health research in an African context.

3.1.3 Basic ethics codes of behaviour

The following should apply to any research programme:

i. ***The participant as a person***

Respect for the autonomy of the participant, whether patient or volunteer, demands that the participant must be treated as a unique human person within the context of his or her community system. Freedom of choice must be safeguarded.

ii. ***Human rights***

Respect for the basic rights of the individual as a human being as well as the rights of groups and communities.

- iii. ***The ethic of justice, fairness and objectivity***
Research should always respect the dignity of people involved and should never expose them to intentions and motives not directly attached to the research project, its methodology and objectives.
- iv. ***Competence***
Researchers must be professionally and personally qualified. In all circumstances they must be accountable and act in a responsible manner. Professional standards should be upheld in accordance with academic training.
- v. ***Integrity***
Integrity should be promoted by being honest and fair. Researchers must be honest about their own limitations, competence, belief systems, values and needs.
- vi. ***Sensitivity***
Sensitivity in research implies balancing scientific interest (the research) with general values and norms affecting the human dignity of the people involved.
- vii. ***Confidentiality***
Confidentiality must be respected under all circumstances. Documentation should be safeguarded and viewed as strictly private in terms of the limits set by the research project.
- viii. ***Demarcation of roles***
There should be mutual understanding of the roles and interests of investigators and participants in research.
- ix. ***Communication***
Clear and understandable verbal communication is required, with factual data. Emotional and cultural values should be considered.
- x. ***Possible dangers to be taken into consideration***
 - o ***The danger of objectification and fragmentation***
Special care must be taken not to treat a participant as a mere object. Research objectives are subordinate to the following principle: to treat human beings with respect.
 - o ***The danger of direct or indirect coercion***
Direct or indirect coercion of people in the name of research must be avoided under all circumstances. Coercion may include the exploitation of vulnerable people; taking undue advantage of a participant, volunteer or any other person; or the misuse of the authority and influence of the research.

4. The medical justification for research

4.1 Healthy volunteers

Research on healthy volunteers is required to gain knowledge in two main fields, outlined below.

4.1.1 Human biology and psychology

Further knowledge of human biology and psychology is important in its own right and also because it increases understanding of disease. Research may be by observation or experiment.

4.1.2 Medicines, cosmetics, medical devices and other agents

- 4.1.2.1** New medicines intended for human use need to be tested in humans to discover whether they are effective and safe, and to determine appropriate dosages. The response to drugs in humans may be different from that in laboratory animals.

- 4.1.2.2** It may be argued that it is more ethical to test medicines on patients who might benefit, rather than on healthy volunteers, but there are advantages in doing initial studies on healthy volunteers. In healthy persons there is less physiological variation and their responses are likely to be more uniform. Healthy persons are often better able to collaborate in more complex experiments, and the ethical dilemmas of treatment with an inadequate dose, or of withholding potentially effective treatment, do not arise.
- 4.1.2.3** Where harmful effects of a medicine may be expected at therapeutic dose levels, it is unethical to use healthy volunteers. With certain drugs, such as those for cancer or leukaemia, it is necessary to undertake initial studies on patients who might benefit.
- 4.1.2.4** Cosmetics and other substances, such as domestic washing powders used on or by humans, may need to be tested on healthy volunteers.

4.2 Patients (See also 6.1)

Much important health research is carried out in non-clinical laboratories and some research into novel treatments requires prior testing in animals, but the ultimate test of the effectiveness, safety and relevance of clinical procedures, investigations and treatments is whether they can be shown to be of benefit in patients. The aim of research on patients is to benefit the individual and/or society. Research on patients falls into five main categories:

4.2.1 Causes of disease

The individual patient usually does not benefit from the results of such research. The character of the research may vary greatly, from non-intrusive epidemiological studies to surgical removal of tissue for examination. In the latter case, patients are necessarily intimately involved and there is a clear need to protect them from unwillingly or unwittingly being subjected to discomfort or hazard. Epidemiological studies usually involve no risk of bodily discomfort or harm, but issues of privacy and confidentiality may arise and special safeguards may be necessary.

4.2.2 Improvement of the diagnosis or assessment of disease

The bulk of research intended to improve the diagnosis or assessment of disease inevitably involves the personal participation of patients and takes a variety of forms. Patients do not usually benefit directly and, if they do, this may be no more than a fortunate by-product of the research.

4.2.3 Improvement of the treatment of disease

Before new medicines are given to patients, they are commonly tested in animals and, usually, also in healthy volunteers. However, to determine their value and safety they must eventually be studied in patients who need them. It is normally necessary to compare the outcome in a large number of patients, some of whom receive the new treatment and some of whom receive standard treatment (control patients). Some trials may also require the use of inert or placebo preparations for comparison.

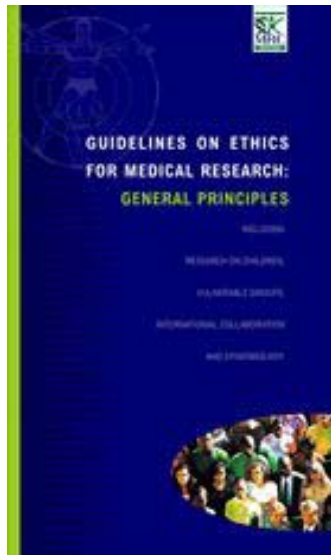
4.3.4 Health care in communities

Patients have an essential role to play in studies designed to assess the effectiveness of health care, even when novel treatments are not involved.

4.2.3 Basic human biology

Much research into the functioning of the human body and mind involves healthy volunteers and is based on the study of the whole individual, or of tissues or body fluids. Sometimes the

study of patients who have a particular abnormality, or who are undergoing a diagnostic or therapeutic procedure, may be the only means of obtaining new information about human biology. Benefits that result from the new information may be obvious in terms of their potential application to the development of new diagnostic tests or treatments. Sometimes, however, the information may be considered worth seeking as an addition to overall understanding with only an uncertain, remote or indirect chance of benefit to patient care.



5. The legal and moral justification for research

5.1 Consent is essential

Section 12(2)(c) of the Constitution of South Africa Act, No 108 of 1996, states: ' Everyone has the right to bodily and psychological integrity, which includes the right... not to be subjected to medical or scientific experiments without their informed consent'. A literal interpretation might mean that only competent persons who are capable of giving consent to clinical research, whether therapeutic or non-therapeutic, interventionist or observational, may be research participants. However, this Section may be interpreted more flexibly (taking account of other existing South African legislation) to allow therapeutic research on an incompetent person to be carried out with the consent of someone acting lawfully on that person's behalf (proxy consent), since such research is of potential personal benefit to the person involved.^a

The wording used in the South African Constitution is identical to that used in the United Nations Covenant on Civil and Political Rights (1966), which is binding on the states that are party to it. It may therefore be argued that section 12(2)(c) may be interpreted in a fashion similar to the interpretation given to the Covenant by those states. This approach would entail that non-therapeutic research (see also 5.3.1.1.1) on an incompetent person might be permissible in limited instances, but only with the consent of someone who is legally authorised to act on that person's behalf, and provided that the incompetent person gives his or her assent. Assent implies a willingness that does not necessarily carry the greater understanding and legal implications that are generally understood by 'consent'.

While non-therapeutic intervention research is not permissible, observation research of a non-therapeutic and non-invasive nature might be permissible because there is no risk and no interference with the mental or physical integrity of the participant, provided that the research entails no more than negligible distress or discomfort to the participant.^b

Observation research of a non-therapeutic and invasive nature might also be permissible, provided that no more than negligible risk is foreseeable or known from routine clinical practice and that distress or discomfort is negligible.

To avoid the difficulty of obtaining consent, clinical research of no benefit or little benefit to the incompetent person is sometimes labelled as 'therapeutic'. However, all types of clinical research on incompetent people should be presumed to be non-therapeutic. This ensures that such research is subjected to strict scrutiny and conditions, and that incompetent persons are not abused or unduly influenced for research purposes.

5.2 Form of consent

In the absence of compelling reasons to the contrary, written information and consent forms should be the norm for health research interventions.

5.3 Requisites of consent

5.3.1 Capacity to consent

Consent must be given by someone who is legally and factually capable of consenting. Where a person, on account of age or physical or mental condition, is incapable of consenting to the proposed research procedure, proxy consent (consent by someone who is legally authorised to act on behalf of the incompetent person) must be procured. With regard to competence to consent and proxy consent, two broad categories of research participants must be distinguished.

5.3.1.1 Adults

Provided they are sane and sober, adults have the capacity to give valid consent to clinical interventions. Categories of adults whose competence to consent could be compromised under certain circumstances, are the following:

5.3.1.1.1 *The mentally ill or mentally handicapped*

Section 60A of the Mental Health Act, No 18 of 1973, provides for consent to clinical interventions (which would include research of a therapeutic nature) on institutionalised mentally ill patients. It provides that where a mentally ill patient is incapable of consenting to medical treatment or to an operation, the following persons, in order of precedence, may give written consent to the treatment or operation: a curator, the patient's spouse, a parent, a major child or a brother or sister. In the absence of such persons, or where they cannot be found after reasonable inquiry, the superintendent of the hospital where the patient finds himself or herself may give written consent. The superintendent must be convinced, on reasonable grounds, that the patient's life is in danger or that the patient's health is being seriously threatened by his or her condition, and that the treatment or operation in question is necessary.

Section 60A confirms the viewpoint that the individual mentally ill patient's competence to consent to medical treatment or to an operation depends upon whether, in fact and in the circumstances, the patient has the ability to appreciate the issues involved.

Section 60A, however, does not cater for consent to the medical treatment of, or an operation on, a mentally ill patient who is not institutionalised, but is in private care and has neither a curator nor relatives to consent on his or her behalf. Under these circumstances, an application should be made to the High Court for the appointment of a curator.

Should a mentally ill or mentally defective (incapacitated) patient be incapable of consenting to therapeutic research, proxy consent is permissible only where the proposed research pertains, directly or indirectly, to the mental illness or mental defect from which the patient suffers. In addition, the assent of the patient should be obtained, provided that the patient is mentally able to comprehend the issues involved.

Non-therapeutic research on incapacitated persons would not be permissible, with the following exception: proxy consent may be obtained for:

- i. observation research of a non-therapeutic and non-invasive nature, as there is no risk and no interference with the integrity of the incapacitated person, provided that the research entails no more than negligible distress or discomfort to the incapacitated person involved;
- ii. observation research of a non-therapeutic and invasive nature, provided that normally no more than negligible risk is foreseeable or known from routine medical practice, and that distress and discomfort are negligible.

In addition to the above, the following requirements must be met in non-therapeutic research:

- i. the research pertains, directly or indirectly, to the mental illness or mental defect from which the person suffers;
- ii. the assent of the person is sought and heed is given to his or her wishes expressed in any advance directives. An objection by the incapacitated person is decisive;
- iii. research involving incapacitated persons significantly benefits persons of the same category as the research participant;
- iv. the same scientific results cannot be obtained by other methods, or by research on persons who do not belong to this category.

5.3.1.1.2 The elderly

Old age alone does not render a person incapable of consenting to health research. In the absence of any indication to the contrary, elderly patients are generally assumed to be competent to consent to research. However, consideration should be given to the possibility of mental deterioration, the ability to comprehend, and the dependence and vulnerability of the elderly.

5.3.1.1.3 Pregnant women

Pregnant women are usually competent to consent to health research, but the circumstances may sometimes compromise their decision. Where possible, the father of the unborn child should be included in making the decision.

5.3.1.1.4 Unconscious patients

Unconscious persons are obviously incapable of consenting to anything, but provided

- i. there are no indications to the contrary and
- ii. the informed consent of a competent relative is obtained, therapeutic research on an unconscious patient is legally permissible. With regard to non-therapeutic observation research, their position is similar to that of mentally ill or mentally handicapped persons (see also 5.3.1.1.1).

5.3.1.1.5 The dying

The capacity of the dying to consent to health research depends upon the circumstances of each case. Special consideration should be given to their vulnerability and dependence in any attempt to procure their consent to health research.

5.3.1.1.6 Members of vulnerable communities (see also 11)

5.3.1.2 Minors

5.3.1.2.1 Competent minors

In terms of Section 39(4) of the Child Care Act, No 74 of 1983, and in the absence of specific legislation to the contrary, minors who have attained the age of 14 years are legally capable of consenting to medical treatment of themselves and their children. Minors who have attained the age of 18 years are legally capable, in addition, of consenting to medical operations upon themselves. Such consent is valid only where the minor is sane and sober. The consent of a parent or legal guardian is required for treatment if the minor is under the age of 14 years, and for an operation if the minor is under the age of 18 years. In the event of conflicting views between the child's father and mother, the child's best interest settles the matter. 'Medical treatment' is not defined in the Act, but would probably exclude non-therapeutic medical research. Therapeutic research, therefore, may be undertaken with the

consent of a minor over the age of 14 years if it takes the form of treatment, and with the consent of a minor over the age of 18 years if it involves an operation. Such minors' competence to consent accordingly extends to health research which is tantamount to treatment or an operation and, hence, to therapeutic research only. (In addition, consent from a parent or legal guardian is desirable.)

Non-therapeutic research on minors is not permissible, except where parental consent (and the assent of the minor concerned) is obtained for:

- i. observation research of a non-therapeutic and non-invasive nature, because there is no risk and no interference with the integrity of the minor, provided that the research entails no more than negligible distress or discomfort;
- ii. observation research of a non-therapeutic and invasive nature, provided that normally no more than negligible risk is foreseeable or known from routine clinical practice, and that the distress or discomfort is negligible. (See also 9.12.4.1)

5.3.1.2.2 Incompetent minors

Proxy consent to therapeutic research on incompetent minors under 14 years (to treatment) or under 18 years (to an operation) must be obtained. Furthermore, the assent of the minors must also be obtained, provided they are mentally able to comprehend the issues involved. The research should pertain, directly or indirectly, to the illness or disease from which the child suffers.

Where non-therapeutic research is involved, proxy consent may be obtained for the following:

- i. observation research of a non-therapeutic and non-invasive nature, because there is no risk and no interference with the integrity of the minor, provided that the research entails no more than negligible distress or discomfort to the minor;
- ii. observation research of a non-therapeutic and invasive nature, provided that normally no more than negligible risk is foreseeable or known from routine clinical practice and that the distress or discomfort is negligible. (See also 9.12.4.1)

In addition to the above, the following requirements must be met in non-therapeutic research:

- i. the proposed research pertains, directly or indirectly, to a condition from which the minor suffers;
- ii. the assent of the minor is sought and his or her objection is regarded as decisive;
- iii. research involving minors significantly benefits minors of the same category as the research participant;
- iv. the same scientific results cannot be obtained by research on persons who do not belong to this category, or by other methods.

All types of clinical research on minors are presumed to be non-therapeutic. This avoids labelling clinical research of little or no benefit to the minor as 'therapeutic'. This ensures that such research is subjected to strict scrutiny and conditions, and that minors are not abused or unduly influenced for research purposes.

5.3.2 Informed consent

5.3.2.1 The nature and scope of adequate information

Research participants, or persons giving proxy consent, cannot give informed consent unless they know and appreciate what it is they consent to. To attain this, adequate information must

be provided.

5.3.2.2 Participant autonomy

The requirement that consent in the health context must be informed consent is customarily associated with the so-called 'doctrine of informed consent'. This means that autonomy is a participant's fundamental right and rejects investigator paternalism. According to the doctrine, the ultimate decision to participate (informed consent), to refuse to participate (informed refusal), or to withdraw from an intervention, lies with the participant and not with the investigator. The doctrine of informed decision requires that the participant should understand the risks and benefits of the study before making that decision, whether positive or negative. The right to refuse may be acted on at any stage, even before the explanation of risks and benefits.

Within the context of health research the paternalistic 'participant's best interest' and the 'researcher knows best' attitudes are inappropriate.

- i. The undeniably inherent potential for abuse of research participants requires a stricter adherence to the requirement of informed consent in health research than in standard practice.
- ii. The absence of personal benefit to the participant who consents to non-therapeutic research requires a stricter adherence to the requirement of informed consent in non-therapeutic research than in therapeutic research.

5.3.2.3 Nature, scope and limitations of the investigator's duty of disclosure

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 treatments in the case of therapeutic research.

Full disclosure means that the investigator informs the research participant, or person giving proxy consent, that the proposed investigation involves research. The investigator gives the research participant, or the person giving proxy consent, comprehensive and detailed information in understandable language about the following:

- i. the precise nature, scope, purpose and duration of the proposed research project. That is, whether it is therapeutic, non-therapeutic, invasive, observational, a pilot study, controlled, randomised, single blind, double blind, triple blind or quadruple blind, and whether or not placebos are involved;
- ii. the nature, scope and consequences of the proposed research intervention;
- iii. the anticipated benefits and disadvantages compared to those expected from available standard therapy;
- iv. the foreseeable prognosis and all foreseeable and additional risks, dangers and complications, as well as the possibility of unforeseen risks, dangers and complications, irrespective of whether the proposed research is therapeutic or non-therapeutic;
- v. personal benefits, including financial benefits, that may accrue from the research to participants, investigators and anyone giving proxy consent. Moreover, the research participant, or the participant's proxy, should be informed that participation is voluntary and that he or she is:
 1. under no obligation to consent to the research procedure and that a refusal will not adversely affect future treatment;
 2. free to withdraw consent at any time without adverse consequences and without having to state a reason.

Evidence suggests that the combination of written information supplemented with face- to- face interaction is the most desirable method of ensuring an informed decision.

In addition, the research participant, or the participant's proxy, should be given sufficient time to contemplate and decide on participation in the research project.

This leaves little room for therapeutic privilege or waiver of information as justifications for non-disclosure in cases of therapeutic research. Information should be given, even if the investigator takes the view that disclosure of the risks and dangers in such circumstances is unnecessary or undesirable.

In cases of non-therapeutic research, there is thus no room at all for therapeutic privilege or for waiver of information.

5.3.2.4 Free and voluntary, clear and unequivocal, comprehensive, revocable

Consent to health research must be free and voluntary, clear, unequivocal and comprehensive. It may be withdrawn at any time, without any reason being given.

5.3.2.4.1 Free and voluntary consent

Consent may not be induced by fear, force, threats, duress, coercion, compulsion, deceit, fraud, undue influence, perverse incentives or financial gain. There are categories of persons in whom the voluntary nature of consent may be compromised. These include prisoners and soldiers, students and employees, and other individuals in dependent relationships (see also 5.3).

Regarding prisoners and soldiers, the mere fact that someone is incarcerated or is a subordinate, does not render them legally incapable of consenting to research. However, the potential for abuse of the incarcerated and subordinated, who are either involuntarily detained or subjected to a hierarchical and authoritarian dispensation, may raise serious doubt about the required voluntary nature of their consent. This extends to information routinely collected from all prisoners without informed consent.

Regarding students and employees, due care should also be taken that their voluntary participation in health research is in no way compromised by their position. Other subordinate groups to be considered are listed in 5.3.

5.3.2.4.2 Clear and unequivocal consent

The expression is self-explanatory and needs no amplification.

5.3.2.4.3 Comprehensive consent

Consent must extend to the entire research proposal, inclusive of its potential consequences.

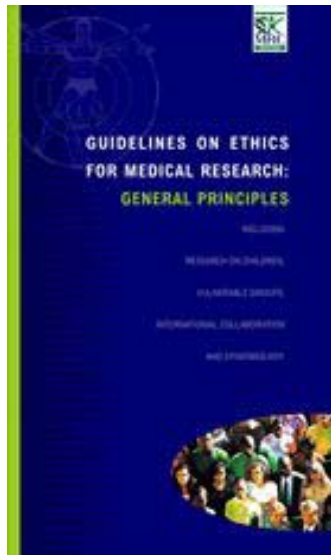
5.3.2.4.4 Revocable consent

Consent may be withdrawn without prejudice, in any form, and at any time prior to and during the proposed intervention.

5.4 Participant's friend

Investigators are responsible for procuring the informed consent of the research participant or person acting on his or her behalf, but it may sometimes be appropriate to appoint a special, informed person to act as an independent source of information and advice. This so-called 'research participant's friend' is not actively involved in the particular research project, but is

an experienced clinician who acts in the interest of a research participant. This is a clinician who is not involved in treating the patient, is not a participant in the research, and acts as a neutral advisor to the patient or the patient's curator or relative. The concept of participant's friend helps to ensure understanding of what is required for participation in the research.



6. Conduct of research

6.1 Responsibility for overall care of patients

- 6.1.1** In most cases the person who approaches the patient to be recruited should be the clinician responsible for the routine clinical care of the patient. Where patients are the research participants, the investigator conducting the research project may or may not be the same person as the clinician responsible for their overall care. It may therefore happen that changes in management will be undertaken only with reluctance, for fear of disturbing the research procedure. Alternatively, the usual clinician may not realise that he or she retains overall responsibility for care, being under the illusion that the researcher had taken over this role. Proper communication is essential between all health care workers and investigators who share responsibility for the care of the patient.
- 6.1.2** It is important that the ordinary requirements - clinical and other - are not neglected as a consequence of the involvement in research, and that the identity of the person in overall clinical charge of the patient's care is clear. This person should know about the research and be in agreement with it. If there is any likelihood that the patient might be confused about which clinician is responsible for overall care, this should be made clear on the Participant Information Sheet.

6.2 Responsibility in the conduct of multicentre studies

In multicentre studies it is particularly important that the person responsible for the overall clinical care of the patient should be closely concerned with, or informed of, the running of the research project. His or her agreement should be obtained. This avoids uncertainty on the part of others in the clinical team, if there seems to be conflict between the apparent demands of the research protocol on the one hand, and the interests of the individual patient on the other. The patient's interests take precedence at all times.

6.3 Delegation and research conducted by non-medical health-workers

Where research activities will be delegated by the investigator, the Research Ethics Committee should be satisfied that the investigator will delegate only to individuals with the necessary skills and experience.

Research ideas and projects increasingly emanate from non-medical groups of health workers. In many instances the responsibility for the conduct of the research may be entirely that of the investigating health worker. In most instances, however, it may be necessary to obtain the consent of the relevant clinician for any planned research intervention to ensure that this is appropriate to the patient's state. The collection of samples (or information) from patients should be supervised by the relevant clinician or a skilled person nominated by the clinician.

All research involving patients must be referred to a Research Ethics Committee. In some cases, class approval may be given in advance to applications for minor research or a series of studies of a particular type to be carried out as a regular feature of a research or training programme. Even in these circumstances, the Committee will wish to be informed of each individual study by title at least.

6.4 Responsibility for the welfare of research workers and laboratory personnel

- 6.4.1** The Research Ethics Committee should stress the importance of safeguarding the welfare of all personnel participating in research. The primary investigator must formulate and apply safety rules and guidelines for the handling of all hazardous materials. The provisions of the Occupational Health and Safety Act, No 85 of 1993, regarding a safe working environment, should be adhered to.
- 6.4.2** Arrangements for compensation in the event of injury should be dealt with as outlined in the recommendations of Good Clinical Practice.⁹ Occupational injury should also be compensated in accordance with the Occupational Injuries and Diseases Act, No 130 of 1993.

6.5 Adequacy of facilities to carry out research

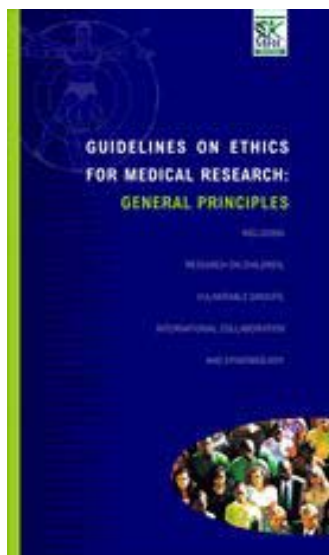
Where there is doubt about the appropriateness of the facilities in which research will be done, a site visit by representative members of the Research Ethics Committee may be necessary.

6.6 Participant privacy and confidentiality

The right to privacy - which includes autonomy over personal information - is a common-law and constitutional right. It means, for example, that clinicians have a duty to ensure that information concerning their patients remains confidential. Failure to safeguard information may render a clinician liable for breach of confidentiality. Legal exceptions may be imposed in terms of the law, as where clinicians may be obliged to disclose information regarding notifiable diseases. Disclosure may also be made where the patient concerned has consented to disclosure.

- 6.6.1** It is essential that information about a research participant, whether a patient or a healthy volunteer, should be regarded as completely confidential. This is the case where the information is derived from the medical records or from research activity. Sensible precautions should be taken to preserve confidentiality.
- 6.6.2** Ideally, no names of persons participating in a study should be on a research record. All participants should be coded, and only these codes used to identify individuals and to prevent, for example, double entries. The principal investigator must take responsibility for keeping a control list of names and codes, and see that confidentiality is maintained. The key to the code should be kept secret by the investigator. Where identifiers are needed to link data to a patient or other participant, they should be kept separately from patient records. On completion of the research, these identifiers should be destroyed, and in all further analysis the codes should be used to distinguish data.
- 6.6.3** When the research is complete, the need for confirmed confidentiality and security of information remains.
- 6.6.4** Information about persons participating in a study may be released to a third party only with the consent of the participant or someone legally capable of consenting on the participant's behalf.

6.6.5 Care must be taken to ensure that confidentiality about the identity of participants will be preserved, through the use of coding, for example, when the results of research are published.



7. Research participants

Research may be conducted on healthy volunteers or on patients. Within each broad group a number of special groups require particular ethics consideration.

7.1 Research on healthy volunteers

A healthy volunteer has been defined as an individual who is not known to suffer any illness relevant to the proposed study and who is able to understand and give valid consent to the study.⁴

Although it may be scientifically appropriate to use patients as controls for a condition from which they do not suffer, they should still be regarded as patients. Because of the subtle pressures to which patients may be subjected, great care must be taken in recruiting such volunteers.

Research on healthy people is undoubtedly necessary, but concern for the health, safety and rights of the healthy volunteer must be paramount.

Research on healthy volunteers, as on any research participants, must be carried out with appropriate selection of volunteers, informed consent and proper conduct of research. Where appropriate, compensation for injury should be made in accordance with the principles of the guidelines of the Association of the British Pharmaceutical Industry as adapted for South Africa.¹⁰ (See Appendix IV.)

Appendices I and II are the MRC checklists provided to assist in compiling healthy volunteer information sheets and consent forms.

7.1.1 Therapeutic and non-therapeutic research

By definition, healthy volunteers will not be participants in therapeutic research, but will participate in non-therapeutic research. They will thus not benefit directly from the research in which they participate. The risk to which healthy volunteers are subjected must thus be no more than minimal (see also 9.12.4.3).

7.1.2 Recruitment and selection of healthy volunteers

Recruitment of healthy volunteers for research projects may involve conscious or unconscious pressures on both the investigator and the volunteer. The motives that prompt people to volunteer are various. They may be scientific or idealistic, but there must be no coercion, overt or covert, to induce anyone to volunteer for research.

Initial recruitment should be through circulars, notices and announcements to groups, and not by individual approach. The method of recruitment and source of healthy volunteers should be included in the study protocol submitted to the Research Ethics Committee.

Excessive use of any volunteer should be avoided and study organisers should prevent this by maintaining lists of volunteers.

Conducting research on oneself is not discouraged, but any persons planning to experiment on themselves should seek the guidance of the Research Ethics Committee before starting their research.

7.1.3 Special groups

Special consideration must be given to protecting the welfare of certain classes of research participants; for example, pregnant women, children and adolescents, prisoners, people with mental disabilities and the elderly, students and persons in dependent relationships.

7.1.3.1 Pregnant women

Special attention must be given to non-therapeutic research that involves women who are pregnant or may become pregnant, because of additional health concerns during pregnancy and the risk of damage to the fetus.

The exclusion of pregnant women from research should be adequately justified, both in terms of protecting the health of the fetus and from the perspective that such exclusion is scientifically supportable.

7.1.3.2 Children

Non-therapeutic research on healthy children (under the age of 18 years, according to the Constitution) should be approved only if the research places the child at no more than negligible risk (see also 9.12.4.3). Research that would be equally informative if carried out on adults, should never be done on children. Children should participate only where their participation is indispensable to the research.

There must be no financial or other inducement to participate for parent, guardian or child, although reimbursement of expenses is allowed. A small gift to the child after completion of the research is acceptable.

In all cases assent of the child and consent of the parent or legal guardian must be obtained. A child's objection to participation in research must always be respected (see also 5.3.1.2).

7.1.3.3 Prisoners

It is not inherently unethical to carry out non-therapeutic research on prisoners. However, particular care must be taken to ensure that informed consent is given and that coercion in any form is avoided. It must be made clear that participation in the research will not lead to any favours, such as reduction of sentence, or special privileges. Similarly, non-participation will not have adverse consequences.

Research Ethics Committees must pay attention to any proposal to undertake research on prisoners, to avoid exploitation of these persons. The Committee must be convinced that the research cannot be conducted on another population. If research on prisoners is undertaken, the Research Ethics Committee must be satisfied that it will be done under conditions of safety for all concerned.

7.1.3.4 People with mental impairment

Non-therapeutic studies should not be done on the mentally handicapped if the same information can be obtained from studies on any other group. Research that is likely to benefit

or prevent mental handicap, and is possible only in mentally handicapped people, is acceptable if precautions are taken, similar to those that apply to children (see also 5.3.1.2).

7.1.3.5 The elderly

Particular care should be paid to the elderly participant's ability to comprehend what is entailed in volunteering as a research participant. Because elderly people are often in a position of dependence on caregivers, they must be reassured that failure to volunteer carries no negative consequences.

No research should be conducted on the elderly if the same information can be obtained from research on other adults.

7.1.3.6 Students

Students are particularly vulnerable to academic, personal and financial pressures.

It should be made clear that refusal to participate in, or a decision to withdraw from a non-therapeutic study carries no negative consequences. Equally, it must be made clear that participation carries no hidden benefits. An investigator who is involved in any way in the tuition or assessment of the student, should not participate in the recruitment of that student. Investigators should be aware of, and try to minimise factors such as the desire to please or not displease, to gain favourable notice or promotion.

Reimbursement of expenses and a possible honorarium should be reasonable for the amount of inconvenience, but should not be excessive or unduly influence risk-taking.

7.1.3.7 Persons in dependent relationships (see also 5.3)

Persons whose proposed involvement in non-therapeutic research arises from dependent relationships, need additional attention to ensure that their involvement is voluntary and that their consent is adequately informed. They include those in junior or subordinate positions in hierarchically structured groups such as:

- i. employees and employers;
- ii. wards of State and guardians;
- iii. patients and health care professionals.

Patients should be invited to participate in research as volunteers, in the same way that healthy individuals are invited to participate.

Patients, unlike healthy volunteers, are dependent on clinical advice or treatment, and may feel under an obligation to clinicians. This, and the fact that some patients may have an impaired capacity to understand what is intended, necessitates safeguards to ensure that volunteering is valid and is based on adequate information.

7.1.3.8 Vulnerable communities

The characteristics of a vulnerable community include one or more of the following:

- i. limited economic development;
- ii. inadequate protection of human rights;
- iii. discrimination on the basis of health status;
- iv. inadequate understanding of scientific research;
- v. limited availability of health care and treatment options;
- vi. limited ability of individuals in the community to provide informed consent.

The ethics of research in vulnerable communities and developing countries is of growing concern¹¹ (see also 11).

South Africa is home to a number of vulnerable communities. Particular caution must be exercised before permission is given to undertake research involving such communities. The Research Ethics Committee must be satisfied that the research cannot be carried out in a less vulnerable community, and that the research is responsive to the health needs and priorities of the community in which it is to be carried out. The research protocol should demonstrate some benefit to the community involved, and how feedback on the outcome of the research will be transmitted to the community.

Particular attention must be paid to the content, languages and procedures used to obtain informed consent in vulnerable communities.

7.2 Research on patients

A patient is defined in the research context as someone whose participation in research derives from either:

- i. having sought or accepted clinical care;
- ii. having been selected from the general population because of known or suspected abnormality;
- iii. a control participant suffering from a disease which is not the subject of study.

Although it may be scientifically appropriate to use patients as controls for a condition from which they do not suffer, they should still be regarded as patients. Because of the subtle pressures to which patients may be subjected, great care must be taken in recruiting such volunteers.

The study of disease as it occurs in patients, and of the effects of treatment, are indispensable parts of the continuing process of improving efficiency of diagnoses and effectiveness of treatment. Patients may willingly participate in research: however, a patient is in a position of at least partial dependence which may affect the capacity to volunteer completely freely. In addition, the ability of the patient to give informed consent may be impaired by illness.

7.2.1 Therapeutic and non-therapeutic research (see also 2.1.2)

In most cases, research on patients will be therapeutic research; that is, investigating an intervention that might be of therapeutic benefit to the patient.

In therapeutic research, the benefits likely to accrue to the individual patient participating should outweigh the risk of harm. As a general rule, research involving patients should incur no more than minimal risk unless there is great potential benefit to the individual.

7.2.2 Special groups

Investigators must ensure that research protocols exclude groups that might be markedly more at risk than others, unless their inclusion is absolutely necessary.

Inclusion of an individual or group that may be especially vulnerable - children, for instance - should be approved only if the Research Ethics Committee considers such inclusion to be essential, and that the participation of less-vulnerable subjects would not answer the purpose of the research.

Patients must be made aware that they may decline to participate in a research study, and that they may withdraw from the study at any time without suffering any discrimination or adverse consequences. The patients' decision will be respected and accepted without question, and they will be treated as though the matter had not arisen, without compromising future care.

Those special groups addressed in 5 require the same sort of special consideration whether they are participating in research as healthy volunteers or as patients. One other group requires particular consideration as patients.

7.2.2.1 Persons with cognitive or mental impairment

This group includes people with psychiatric or developmental disorders, or people who are substance abusers. They may have reduced capacity to comprehend the research and to agree to participate in it. Institutionalisation may also compromise an individual's capacity to make a truly voluntary decision to participate in a research study.

Persons with a cognitive or mental impairment should not participate in research that could equally well be conducted on persons without this impairment.

The research must be relevant to cognitive impairment, possible to evaluate only in people with such impairment and likely to benefit or prevent cognitive impairment.

7.2.3 Confidentiality

Any list of patients' names must be confidential to the person responsible for its compilation. Use of a coding system should ensure this. In most circumstances, the person who recruits the patient should be the clinician responsible for the routine clinical care of that patient.

7.2.4 Use of clinical records in research (See also 6.6)

Personal clinical records are a vital tool for much clinical and epidemiological research. Great care must be exercised to protect privacy and maintain confidentiality, to avoid causing harm or distress to patients or their relatives. Research that will involve access to personal health records must receive approval from a Research Ethics Committee.

In general, the researcher should seek the consent of the clinician currently or most recently responsible for the care of the patient, before using the record for research purposes.

In principle it is also necessary to obtain the consent of the patient before the clinical record is used as a source of information for research purposes, especially if the patient's right to privacy might be infringed - by linking the research with the patient, for example. The point at which a record review is decided on has been seen in the past as decisive. Retrospective record analyses may be done without patient consent, provided they are done anonymously, but prospective record analyses require patient consent. However, the better ethical and legal view is that consent should also be obtained, if possible, for retrospective analyses.

Information derived from personal clinical records stored in computers requires the same safeguards as conventional paper-based records. Particular care is required where information from clinical records is transferred to computers that can be accessed by many users.

Since this is a confusing issue, here is some clarification:

The right to privacy - which includes autonomy over personal information - is a common-law and constitutional right. This means inter alia that clinicians must keep confidential all private information pertaining to their patients. Privacy is at stake only when the bearer of the right can be identified through the private information divulged. Clinicians who pass on personalised data to third parties, including research investigators, without the patient's informed consent, may be liable for breach of confidentiality.

In principle the patient's consent to disclosure of named data must be sought, whether the envisaged research is retrospective or prospective in nature. In such instances privacy must be adequately safeguarded, by not allowing unauthorised persons access to the information, for example, and by requiring all investigators involved to sign a confidentiality agreement. Consent may be dispensed with only in exceptional circumstances, such as where the public interest in the information being passed on clearly outweighs the individual interest in privacy.

The law may also oblige clinicians to disclose private information, such as that concerning notifiable medical conditions, to public health authorities. The Promotion of Access to Information Act, No 2 of 2000, gives effect to the constitutional right of access to information held by the State or its departments. An official of a State department in the national or provincial sphere, or a contractor engaged by such department as an independent contractor, may give access to information held by that body. This means, for example, that if the Department of Health has contracted with someone to act as an independent contractor, this contractor may give access to data (concerning notifiable medical conditions, for instance) held by the Department, if all the requirements of the Act are met. Access to records will be refused if it might involve the unreasonable disclosure of personal information about a third party, including a deceased individual. However, even such unreasonable disclosure of information may be warranted if the individual consented to the disclosure, or had been informed by the public body before the information was given, that the information belonged to a class of information that would or might be made available to the public. Unreasonable disclosure may also be warranted if the public interest clearly outweighs the potential harm resulting from disclosure of the information.

When patients are asked to consent to the use of their records or personal information in research, they should be informed whether (i) their coded information will be used for research purposes (which will be the first option), or (ii) their named information will be used for research purposes, and, if so, which safeguards will protect their privacy. In general, all patients or participants should be informed of confidentiality procedures as part of the consent process. This would apply to both category (i) and (ii) research. Coded information should preferably be used. Codes should be used to distinguish between patients and participants. Where identifiers are needed to link data with a patient or research participant, they should be kept separately from the individuals' records. Upon completion of the research, these identifiers should be destroyed.

Occasionally it may be permissible to dispense with patients' consent to use their hospital or clinic records in prospective record reviews provided that:

1. A risk benefit analysis shows that the public interest in the information being passed on clearly outweighs the individual interest in privacy.
2. All information is normally de-identified, which means that it is not possible to identify a specific individual. Examples of identifiers include the individual's name, hospital number, ID number, date of birth and address.
3. The methods for de-identifying record information are stated and acceptable to a Research Ethics Committee.
4. Individuals de-identifying the records have acceptable training in the de-identifying method acceptable to a Research Ethics Committee.

5. The individuals de-identifying the records have signed a confidentiality declaration acceptable to a Research Ethics Committee.
6. Security standards for the storage and use of the records are acceptable to a Research Ethics Committee.
7. Use of the records is limited to individuals who have signed an acceptable confidentiality declaration and who are approved by a Research Ethics Committee.
8. No one may have access to the de-identified records without approval by the Research Ethics Committee that approved the original record review.
9. Each new use of the information is acceptable to the Research Ethics Committee that approved the original record review.
10. Any financial benefits from the reproduction or use of the information must be openly declared and be acceptable to the Research Ethics Committee that approved the original record review.
11. A complaint procedure regarding use of the records is available.
12. The collection, storage and use of the records fulfil South African legal requirements.

It is the responsibility of the current investigator to ensure that the above criteria are met.

7.2.5 Protection against excessive requests

Some groups of patients, such as those with rare diseases, may be at risk of exploitation through frequent requests to take part in research that may not directly benefit them. Investigators must be sure that such patients, or patients who are readily available and compliant, are not exploited for the sake of convenience and that they do not feel obliged to participate in research as a condition of receiving care.

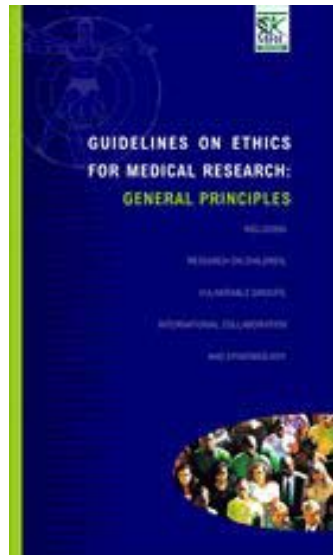
7.2.6 Consultation with other clinical advisers

Where a research project originates in a hospital or other health institution, the patient's personal clinician, under normal circumstances, should be informed of and should agree to the intended research. Only in the case of research of a minor and non-invasive nature need the personal clinician not be informed.

Proper communication is essential between all health care workers who share responsibility for the care of the patient.

7.2.7 The patient as a volunteer

Patients should be invited to participate in research as volunteers, in the same way that healthy individuals are invited to volunteer.



8. Ethics issues in qualitative research

8.1 Introduction

Ethics issues in qualitative research are often more subtle than issues in survey or experimental research. These issues are related to the characteristics of qualitative or field methodology which usually include long-term and close personal involvement, interviewing and participant observation. Field research is an approach based on human interaction, rather than one viewed as outside human interactions. Field investigators themselves are the measuring instruments.¹² There are different stances regarding ethical issues in qualitative research. These include the absolutist stance, relativist stance, contextualist stance and deception model.¹³

The absolutist stance addresses four areas of ethical concern, namely: protection of participants from harm (physical and psychological), prevention of deception, protection of privacy and informed consent. The absolutist stance holds that social scientists have no right to invade the privacy of others. Because the invasion of privacy may cause harm, only those behaviours and experiences that occur in the public sphere should be studied.¹³

The relativist stance states that investigators have absolute freedom to study what they see fit, but they should study only those problems that flow from their own experiences. Agenda setting is determined by personal biography, not by some larger scientific community. The only reasonable ethical standard is one dictated by the individual investigator's conscience. No single set of ethical standards can be developed, because every situation requires a different ethical stance. The investigator is directed to build open, sharing relationships with those investigated.¹³

Within the deception stance an investigator may use any method necessary to obtain greater understanding in a particular situation. This may involve telling lies, deliberately misrepresenting oneself, 'dumping' others, setting people up, using adversarial interviewing techniques, building friendly trust and infiltrating settings.¹³

The contextualist or holistic stance in qualitative research refers to describing and understanding events, actions, and processes in the natural context in which they occur. No attempt is made to generalise to a larger population. Sampling deliberately includes those data sources that are the richest sources of information in a specific context.

8.2 Practical ethics issues in qualitative research

8.2.1 Informed consent^{12,14,15}

Informed consent, from persons capable of such consent, should be obtained as in all other research (see also 5.2). This requires informing participants about the overall purpose of the

research and its main features, as well as of the risks and benefits of participation. Consent may be given in written format, verbally and audio-taped, or videotaped.

If the investigator does not know in advance the questions that a participant might be asked, or what potential risks might be involved in the future, this must be made clear to the participant at the outset.

8.2.2 Responsibility to the participants^{12,14-16}

The investigators' responsibility to the participants includes issues such as ensuring confidentiality, avoidance of harm, reciprocity and feedback of results.

In ensuring confidentiality the investigator may not report private data that identifies participants. One of the safest ways to ensure anonymity is not to record the names of the participants at all and to provide an information sheet that asks for verbal rather than signed consent. Categories of sensitive information requiring anonymity are the following: sexual attitudes, preferences or practices; use of addictive substances; illegal conduct; information that could damage an individual's financial standing, employability, or reputation; medical record information that could lead to stigmatisation or discrimination; any information about an individual's psychological well-being or mental health.

The risk of harm to a participant should be negligible. The sum of potential benefits to the participant and the importance of the knowledge gained should outweigh the risk of harm to the participant and thus support a decision to carry out the research. Qualitative interviews on sensitive topics may provoke powerful emotional responses from a participant. An appropriate referral source for professional help should be ready, should referral be necessary. Such referral may include authorities responsible for responding to illegal conduct.

Ideally there should be reciprocity in what participants give and what they receive from participation in a research project. The investigator is indebted to participants for sharing their experiences. Reciprocity may entail giving time to help out, providing informal feedback, making coffee, tutoring or being a good listener. The reciprocity should fit within the constraints of research and personal ethics, and within the framework of maintaining one's role as investigator. Participants should receive feedback on research results, because this is a form of recognition and gratitude to participants for their participation.



9. Assessment of the ethics of research⁶

9.1 Independent ethical review

All research involving healthy volunteers and patients must be subject to independent ethical review and this should be conducted by a Research Ethics Committee.

9.2 Knowledge of involvement

People who are participants in research, whether they are healthy or sick, must be made fully aware of their position and the nature of the research. This is entrenched in the South African Constitution (see also 5.1).

9.3 Clinician-patient relationship

The clinician-patient relationship is based on the belief that the clinician is concerned to put the interests of the individual patient first. Patients generally believe this, and it is essential that a relationship of trust should be fostered. Lack of truth or frankness about research on the grounds, for example, that the research is harmless and that consent need not be obtained because the process of obtaining it will cause needless anxiety, is a breach of the clinician-patient relationship and the constitutional rights of the patient.

9.4 Role and competence of the investigator^{14,15}

The responsible investigator is appropriately qualified and experienced, and commands facilities to ensure that all aspects of the work will be undertaken with due discretion and precaution to protect the safety of the participants.

Adequate preliminary literature should have been studied, and experimental studies should have been undertaken to define, as far as practicable, the risks inherent in participation, and the investigators should be fully conversant with these.

Ethical issues regarding the role of the investigator include possession of the necessary attributes, competence and the release or publication of results.

The investigator needs two attributes: the sensitivity to identify an ethical issue and the responsibility to act appropriately in regard to such issues.

The character of investigators is critical for the quality of the scientific knowledge and for the soundness of ethical decisions in any research project. The integrity of investigators - their honesty and fairness, knowledge, qualification and experience - are the decisive factors. Investigators have a scientific responsibility to their profession and to participants to ensure that a research project yields knowledge worth knowing and that it is as controlled and well verified as possible. Independence of the research should be demonstrated from the funders of a research project as well as from participants.

The results of the research may be disseminated in written form in both popular and scientific journals. Radio and television broadcasts may also be used. Investigators should compile their research report as accurately and objectively as possible. Shortcomings and errors must be admitted.

9.5 Research Ethics Committees

- 9.5.1** The role of Research Ethics Committees, the history of their origin and details of their composition and organisation, have been provided by the Royal College of Physicians of London.⁶
- 9.5.2** Research Ethics Committees are of crucial importance in the proper regulation of research involving humans and animals, since investigators should not be the sole judges of whether their research conforms to generally acknowledged ethical codes.^{7,17}
- 9.5.3** All research involving humans, whether patients or healthy volunteers, must be referred to a Research Ethics Committee. Sometimes class approval may be given in advance to applications for minor research, or a series of studies of a particular type carried out as a regular feature of a research or training programme. Even in these circumstances, the Committee will wish to be informed of each individual study by title at least.

9.6 Objectives⁶

- 9.6.1** The objectives of Research Ethics Committees are the following:
 - i. to maintain ethical standards of practice in research;
 - ii. to protect research participants and investigators from harm or exploitation;
 - iii. to preserve the research participant's rights, which take preference over society's rights;
 - iv. to provide reassurance to society that this is being done.

In promoting these objectives, Research Ethics Committees should remember that research benefits society and that they should take care not to hinder it without good cause. Investigators should be helped to achieve a high standard of research ethics, if necessary by being provided with basic training in research ethics. Research Ethics Committees also protect investigators from unjustified criticism. International guidelines on human research⁷ indicate that a Research Ethics Committee should consider that:

- i. the objectives of research are directed to a justifiable advancement in knowledge compatible with prevailing community interests and priorities;
- ii. interventions are justifiable in terms of these objectives.

9.6.2 The Research Ethics Committee should see to it that the responsible investigator is appropriately qualified and experienced. The Research Ethics Committee should also ensure that:

- i. Adequate preliminary literature has been consulted and experimental studies have been undertaken.
- ii. Every reasonable effort has been made to inform prospective participants of the objectives and consequences of their involvement and particularly of identifiable risks and inconvenience. Informed consent should be obtained, as outlined in 5.1.
- iii. Any arrangement to delegate consent has adequate justification, and that appropriate safeguards have been instituted to ensure that the rights of participants will not be abused.
- iv. Appropriate measures have been adopted to ensure the confidentiality of data generated in the course of research, through the use of coding or anonymity of participants, for example.
- v. Every effort has been made to ensure that participants have an opportunity to comment on and, if they wish, to decline to participate, or to withdraw from a research project easily - without having to give a reason, and without any adverse consequence.

9.6.5 It is important to be continuously aware of the need to avoid impeding good research. Indeed, the Research Ethics Committee should seek to facilitate valid research in all possible ways, including the provision of training in research ethics and informed consent.

9.7 Scientific misconduct

9.7.1 A Research Ethics Committee should investigate allegations of scientific misconduct and report the findings to an appropriate body for action, such as an employer or research sponsor.

9.7.2 Following world-publicised cases of misconduct in science in recent times, concerns about integrity in the conduct of research, and about misconduct in science, have been extensively debated. The United States National Academy of Sciences, National Academy of Engineering and Institute of Medicine have jointly published the first of two volumes on Responsible Science: Ensuring the Integrity of the Research Process.¹⁸ In this report, specific actions are described which scientists, their institutions and their sponsors can take to preserve and strengthen the integrity of the research process and to deal with allegations of misconduct. The basic sentiments expressed in the report are encapsulated by the President of the National Academy of Sciences: 'Ensuring the integrity of the research process is one of the fundamental obligations that accompanies the right to search for truth'. It should be noted that two of the 22 distinguished panellists who produced this report have expressed general concerns that preclude their support of the report. These dissenting views, seen in the context of the bibliography provided - a condensed version of more than 1400 referenced items in the panel's project files - illustrate the complexity of the issues involved and the need for awareness and ongoing open debate on issues crucial to preserving the integrity of research. Background to research misconduct is given in a publication by the Royal College of Physicians of Edinburgh.¹⁹ A conclusion reached is that only demonstrable compliance with good practice, with appropriate training, and with quality assurance of all research activities will address this issue and ensure the quality of all research data.

- 9.7.3** Investigators have a duty to report perceived research misconduct (falsification, fabrication, plagiarism and departure from ethics standards); institutions have a duty to speedily and fairly investigate this with due transparency and regard for the reputations of whistle-blower and respondent according to the policy of the institution. Whistle-blowers who make allegations in good faith must be protected against retaliation. Examples of model procedures may be found at the Office of Research Integrity website (<http://www.ori.dhss.gov>).

9.8 Function of Research Ethics Committees

9.8.1 Applications for approval

Committees deal with applications from named individuals. Applications should come before the Committee in written form. The Committee's attention is focused primarily on:

- i. the nature of the proposed research activity. The question of the extent to which scientific quality, design and conduct of a research project should be considered by a Research Ethics Committee continues to cause difficulty. Badly planned, poorly designed research that appears unlikely to produce useful or valid results, is unethical. Full scientific evaluation is beyond the capacity of most Research Ethics Committees, and therefore such committees should not hesitate to make use of external advisers for difficult problems, particularly in the areas of design and statistical evaluation of protocols. Ideally, applications for ethics clearance should be submitted only after evaluation of the scientific quality of a project by a body competent to evaluate it;
- ii. the possibility of harm coming to the participant. The application should describe possible risks or side effects;
- iii. the possible benefits of the proposed research;
- iv. consent: how the participant is to be informed about the proposed research and the precise way in which consent is to be sought (see also 5.1);
- v. risk (or cost) benefit evaluation of the proposed research.
- vi. In international collaborative research, the research proposals should conform to both South African and international guidelines, and indigenous communities should not be exploited.

9.8.2 Interview of applicants

The Committee may need to interview investigators. Personal contact with the Research Ethics Committee may clarify queries and confusions more rapidly than written communication. Investigators should have ready access to members of a Research Ethics Committee to obtain help prior to submitting a proposal for approval, or to the Committee itself in order to speed up and facilitate the process.

9.8.3 Terms of reference and scope⁶

A Research Ethics Committee should:

- i. advise its appointing authority on all matters pertaining to the ethics of research involving humans or animals;
- ii. review proposals for human or animal research to be carried out in the institution or area of that authority;
- iii. review proposals for human or animal research to be carried out by staff of the authority in places where there is no Research Ethics Committee;
- iv. not undertake functions that might conflict with the above. For instance, it should not act as a research-funding or grant-giving committee;
- v. make an annual or more frequent report to the appointing authority, and make the report available to the public;

- vi. monitor progress and problems that may be experienced in the conduct of research;
- vii. react to any allegations of misconduct in research involving humans carried out by individuals within the Committee's area of authority.

(For details on Research Ethics Committees for Research on Animals, see Book 3.)

9.8.4 Cost of research

Although the allocation of resources has ethical implications, and consideration of this aspect of research should be given due attention, it is not the prime task of Research Ethics Committees. The fact of ethics approval does not imply that resources ought to be provided, and Committee approval should not be used to assert this.

The results of health, social or environmental research might later give rise to demands for costly implementation. However, this is not properly a concern in the decision made by a Research Ethics Committee on whether the research may ethically be undertaken. Such matters are, of course, a legitimate ethical concern for those responsible for allocation of scarce resources.

What is of concern to a Research Ethics Committee in an environment in which research resources are scarce, is proposed research that is expensive and out of balance with likely benefits. This imbalance implies low beneficence and limited justice in the allocation of resources, and such research should not be granted ethics clearance. Coupled to this is the use of hospital resources to do clinical research of a particular condition, when the treatment of such patients would not normally use those resources. In such circumstances, funding for the extra investigations or treatment must be obtained from sources other than those supplying the hospital.

9.8.5 Ethics of clinical practice⁹

From time to time a Research Ethics Committee may be approached by a clinician with an ethical problem in clinical practice, not of research. Research Ethics Committees are not constituted for this purpose, and it is unwise for a Committee to respond formally to requests that are outside its terms of reference.

9.9 Membership of the Committee

9.9.1 Principles

9.9.1.1 Two principles should determine membership of Research Ethics Committees.⁷

- i. Committees should command the technical competence and judgement to reconcile the physical and psychological consequences of participation with both the welfare of the research participants and the objectives of an investigation.
- ii. Committees should also, with advantage, accommodate respected lay opinion in a manner that provides effective representation of the non-clinical community as well as clinical interests. Lay opinion in the non-clinical community means opinion from a lawyer, social worker, religious leader, teacher or similar person of standing able to contend with pressures from individuals within the broad health profession.

9.9.1.2 Members of Research Ethics Committees should be people of goodwill, with a high regard for the human personality, for truthfulness and for the continued advance of science in the interests of society.

9.9.1.3 It is important that members of Research Ethics Committees should look at applications critically from the participants' point of view.

It is also important that the community should have confidence in Research Ethics Committees. The composition of such a Committee and how to contact members should be public knowledge.

Experience has shown that non-clinical members are invaluable, particularly on issues of consent and information to participants. A non-clinical member with legal training can be of great value, but his or her role should be a general one, not solely to answer questions of law.

9.9.2 Composition of Research Ethics Committees

Ideally, membership of a Research Ethics Committee should include:

- i. Clinical members, including experienced clinical researchers, and at least one general practitioner. A majority of the clinical members should be involved in providing clinical care;
- ii. At least one nurse, preferably in active practice with patients;
- iii. At least one person not practising or trained in any health discipline;
- iv. Both sexes, and individuals of different race groups;
- v. One or more representatives with knowledge of law, pharmacology, qualitative research and statistics;
- vi. One member from outside the institution if clinical trials are being scrutinised according to international norms of Good Clinical Practice (GCP);
- vii. Representatives of disadvantaged communities where research is to be carried out in such communities.

The Committee should elect its own Chairperson from among its members, and a Deputy Chairperson should be elected when the need arises. The Committee should be of manageable size with a quorum of not less than five members. It is not practical that the Committee should include specialists in all the fields of health and science of the various proposals that may come before it. All research projects that involve animals should also be referred to a separate Ethics Committee for Research on Animals (see Book 3).

9.9.3 Co-option

The Research Ethics Committee should have the power to co-opt additional lay or professional advisers for an individual application or meeting.

9.9.4 Appointments

After taking appropriate advice, the responsible authority shall formally appoint the Research Ethics Committee members. It is essential that members serve on the Committee as individuals and not as delegates taking instruction from other bodies or reporting to them.

9.9.5 Duration of membership

The period of membership may be prescribed, such as from three to five years, which may be renewed. It should be remembered that although the Committee should not stagnate, members need time to absorb the ethos and to develop skills of ethical review, and it is important not to lose a valuable and willing member simply because time has passed.

9.9.6 New members

Pending general arrangements for training, new members should be provided with appropriate core literature.

9.9.7 Administrative support

A Committee will require substantial administrative help, including secretarial help. Providing this help must be the responsibility of the appointing authorities.

9.10 Method of working⁶

9.10.1 Meetings

Reasonably frequent, regular meetings are essential to allow a Committee ethos to develop. To work entirely or almost entirely by mail, e-mail or by Chairperson's decisions, even if later put before a meeting, is unacceptable. A disadvantage of working by post is that Committee meetings may become so rare that the valuable mutual exchanges between members are lost, and lay members in particular will feel isolated. For these reasons it is inappropriate to seek to conduct all business without meetings.

For all the members of the Committee to be given the opportunity to express their views, it is important that meetings be held according to correct procedure.

9.10.2 Chairperson's approval

The Chairperson may deal with minor matters with or without consulting other members. Outcomes should be reported to, and the papers made available to all members at the next meeting of the Committee. Wherever possible, consensus should be sought between meetings, for example by e-mail.

9.10.3 Class approvals

Multiple projects that vary in detail but conform to the same general pattern, may be given a 'class' approval to avoid repetitive submissions. Examples might include some projects in epidemiology, or in training students, or using archived pathology specimens. This is particularly appropriate for projects that pose no risk of distress or injury to participants. However, a letter should be sent to the Research Ethics Committee for their records, stating that a particular investigation will be undertaken according to the class approval.

9.10.4 Decisions and quorum

It is necessary for a Research Ethics Committee to define the size and membership of a quorum, and to establish conventions for determining decisions. A quorum of five members, including at least one non-clinical member, is suggested to conform to international practice.^{8,9}

9.10.5 Update

Research ethics is a dynamic area, so it is necessary to circulate to the Research Ethics Committee relevant publications on general policy, to ensure that the Committee is kept abreast of developments. Ideally, members of the Research Ethics Committee should be sponsored by the appointing authorities to attend courses or conferences to update ethics knowledge.

9.10.6 Adverse decisions and appeal

Although it is rare for a project to be found totally unacceptable, it is common for projects to be modified after discussion with a Research Ethics Committee. If an adverse decision is made, the reasons should be given to the applicant. Investigators should be made aware that they are entitled to have an adverse decision reviewed and to make written and oral representations to the Committee.

An appeal procedure should be available. For example, in the first instance this should be to the Research Ethics Committee that made the decision. If a decision is still adverse, an institution might get external opinion or set up an ad hoc committee of experts to review the project and decision.

9.10.7 Monitoring

It is generally impractical (even if desirable) for a Research Ethics Committee to monitor in detail the conduct of ongoing investigations, but Committees should not lose contact with those that they have approved. Some form of follow-up is desirable, if only an annual questionnaire to applicants. This should establish whether the project has been completed, abandoned (in which case the reason should be given) or is still in progress. The investigator should certify that the research is still being carried out according to the approved protocol. Any modification of substance to the original protocol must be notified to the Committee and permission obtained. Information on adverse events should be sought.

It is recommended that:

- i. Research Ethics Committees should require investigators in charge of approved research projects to submit a brief report of progress at least annually;
- ii. Investigators should be requested to send an annual list of published reports to the Research Ethics Committee;
- iii. A standard operating procedure for participants and investigators to approach the Research Ethics Committee when there is concern about the conduct of research, should be in place for each Research Ethics Committee. These may be based on the recommendations of the Office of Research Integrity or the Association of the British Pharmaceutical Industry (see <http://www.ori.dhss.gov> and Appendix IV).

Applicants should be told in any guidelines or forms issued that adverse events should be reported within 72 hours of the event.

9.10.8 Sanctions

Research Ethics Committees have no direct sanctions, but if they learn of research being conducted without their approval or in breach of what they have approved, speedy arrangements should be made to interview the investigator. An investigator who bypasses or ignores the recommendations of a properly authorised Research Ethics Committee, creates a potentially serious situation that could make him or her vulnerable to professional disciplinary or even legal proceedings. Where a Committee is dissatisfied with the conduct of an investigation it may withdraw approval, provided full reasons are given. The Committee should then inform the investigator that approval has been withdrawn. The investigation should cease forthwith and the investigator may not then claim that the research had ethics approval. Removal of approval must be made known to the appointing authority who should inform any research sponsors, and to any national ethics body.

9.10.9 Reports

Research Ethics Committees should make a regular report, at least annually, to the appointing authority. In addition to a list of members, number of meetings and any other obviously relevant matters, it should include a list of the titles of projects approved. The reports should be available for inspection by the public. The only exception to public inspection may be to protect commercial interests. However, company names and product trade names may be included with the consent of the company. A full record of such commercial research must, however, be kept by the committee secretariat.

9.10.10 Clinical responsibility

Clinical responsibility for all patients ultimately reverts to the clinicians treating the individual patient, and the clinicians' agreement should be obtained for research conducted on their patients.

9.10.11 Confidentiality

Confidentiality of Research Ethics Committee proceedings (as distinct from decisions) should be preserved because the issues considered are often complicated and delicate. Uninformed or unbalanced publicity could arouse emotions damaging to all concerned, and especially to patients. Moreover, some investigators who have had an original idea fear that this may be passed to others in competition with them.

9.10.12 Declaration of conflict of interest

Just as applicants should declare any conflict of interests, so members of a Research Ethics Committee should declare theirs, such as where an application relates to testing a product of a company to which the member is an adviser. The Chairperson shall decide whether the interest disqualifies the member from the discussion. Where the Chairperson has an interest, a Deputy Chairperson should take his or her place. Anyone with a conflict of interests may not take part in the discussion or decision-making and this should be recorded in the minutes of the meeting. Members with a conflict of interests should recuse themselves when that protocol is discussed.

9.10.13 Research injuries

In the event of a serious research injury to research participants or research workers, the Research Ethics Committee should satisfy itself that a proper inquiry is conducted, and it should consider implications for continuation of the research study. It should also satisfy itself that provision has been made for compensation for injury.

9.10.14 Access to the Research Ethics Committee

Access to the Research Ethics Committee should be available to research participants who may be dissatisfied. It should be the responsibility of investigators to inform research participants of this.

9.10.15 Fees

In the case of direct applications from the private sector, a reasonable handling charge may be made. Members of Research Ethics Committees should not be paid, other than reimbursement of expenditures. If they receive an honorarium, it should be modest and should not be paid by a body having a financial interest in the outcome of applications.

9.10.16 Educational activities

Educational activities in institutions, which include research, may also include administration of drugs and other, sometimes invasive, procedures. These should be put before a Research Ethics Committee.

9.10.17 Publication

When investigators submit their research for publication, they should indicate that the research has been approved by a Research Ethics Committee, and should list the ethics clearance number. Most reputable journals require this. It is unacceptable in principle that an investigator should agree to conditions that may prohibit or impair the chance of publication, although delay may sometimes be inevitable.

9.11 Suggested format for applications to Research Ethics Committees

It is advisable for institutions to have a standard application form or checklist to help applicants

provide information required by the Research Ethics Committee in making a decision. (The MRC application form is provided as Appendices I and II for quantitative research and qualitative research, respectively.)

Prior consultation with a member of the committee should be encouraged, to help applicants anticipate and correct ethics problems before an application is considered. The secretariat should have a list of committee members available for scrutiny by applicants.

9.11.1 All project proposals should state:

- i. the title of the proposed project;
- ii. details of the investigators:
 - o list names, qualifications, positions, departmental addresses, and functions in the proposed research of all investigators;
 - o name of principal investigator;
 - o experience of principal investigator in the field of research concerned;
- iii. place where research is to be undertaken;
- iv. statement of the problem to be studied, the aims and objectives of the research; the hypothesis which is to be generated or tested and the value of getting an answer; and the possible outcome of the research;
- v. the scientific background. If similar work has been done previously, state why it needs to be repeated. If it has not been done before, has the problem been worked out as fully as possible using animals or other alternative research methods?; An overview of applicable literature should be given;
- vi. the design of the study. Give an outline of the proposed project, including methods to be used, and how the results will be analysed. State the likely duration of the project;
- vii. the type of participants. Give details of the method of recruitment for each category (patients, controls, healthy volunteers). Specify whether participants are in a dependent relationship with the investigators, such as students, or whether they are especially vulnerable, such as children or the mentally handicapped;
- viii. substances to be given, such as drugs, special diets, isotopes, vaccines. State route, dose, frequency, precautions;
- ix. samples to be obtained, such as blood, urine, cerebrospinal fluid, biopsy specimens. Give method and frequency of sampling, amount of each sample;
- x. other procedures. Give details, of radiographs, endoscopy, anaesthesia, for example;
- xi. the potential risks and inconvenience to the participants, their estimated probability and precautions to be taken to minimise risks and inconvenience;
- xii. benefits of research to research participant and/or community;
- xiii. the manner in which the participant's consent will be obtained. An information sheet, written in plain language and understandable by a lay person must be provided, whether the consent form be verbal or written. If the consent is to be written, the form must also be provided. Where relevant, translations in languages of the proposed participants will be necessary. These must be the work of a qualified translator.
- xiv. whether the participant's personal clinician is to be informed of recruitment of the participant before the study begins, and whether the participant's consent to such information being passed on to the clinician is a condition of participation;
- xv. the regulatory status under the relevant legislation of any drug or appliance to be used or tested;
- xvi. investigators' 'interests' relating to the study, such as profit, personal or departmental, financial or otherwise;
- xvii. details of any payments to be made during the study;
- xviii. any conflicts of interest.

9.11.2 Other relevant matter

Attach any other relevant matter, such as letters of permission from an institution to do a study, details of payments to participants, copies of advertisements or any other recruiting matter for healthy volunteers or patients.

9.11.3 Testing medicines and appliances

If the study is sponsored by an industrial company there should be an indication of arrangements for compensation and insurance in the event of injury to participants or investigators according to Good Clinical Practice guidelines.^{9,10}

9.11.4 Paediatric projects (see also 5.3.1.2)

9.12 Assessing the value and risks of research

9.12.1 Objectives of research

The Research Ethics Committee and the investigator should be satisfied that the proposed research is relevant or of scientific value. In coming to a decision, the Committee will bear in mind the magnitude of any intrusion and whether or not there is risk to the healthy volunteer, to the patient, or to the community, as well as the likely importance of the information sought.

9.12.2 Routine research in return for financial support

9.12.2.1 Some research involving patients or volunteers is of a routine nature and is undertaken by clinicians because it brings in financial support, rather than because the information being sought is important. These studies must conform to GCP guidelines.^{9,10}

9.12.2.2 In routine research, importance is often restricted to the commercial interests of a manufacturer, in developing a generic formulation, for instance. When an investigator invites a patient or volunteer to participate in research, it is necessary to give reasons why the research is considered worthwhile. The participant should be informed that the clinician will gain financially from the participant's participation.

9.12.2.3 Research Ethics Committees should be alert to the potential for commercial exploitation of participants or communities, and should withhold approval from projects in which this aspect appears to outweigh the scientific value of the research.

9.12.3 The design of the study

Research Ethics Committees should examine the overall design of proposed research that comes before them. While the appropriateness of the scientific design of a study is not the prime concern of the Research Ethics Committee, it is clearly unethical to allow participants to be exposed to inconvenience or risk in the belief that they are contributing to an increase in knowledge when, in truth, there is no likelihood of such increase. Accordingly, the Research Ethics Committees will occasionally need to give detailed attention to such matters as the ability of investigators using quantitative strategies to make valid and reliable measurements. It should also consider whether the study is likely to produce adequate data for statistical analysis, with a reasonable chance of answering the question under examination. To help the Committee to do this, the research proposal should comment on the adequacy of the proposed statistical methods to evaluate the data generated. Attention also needs to be given to the ability of investigators using qualitative strategies to work in a trustworthy manner in data gathering and data analysis. To help the Research Ethics Committee do this, the research proposal should comment on evaluation of data collection and whether the study is likely to advance the body of knowledge on the subject.

9.12.4 Risk/benefit analysis

A key decision in the assessment of proposed research is whether the risk or inconvenience caused to the participant is justifiable in relation to the value of the information sought. This process is sometimes referred to as risk/benefit analysis. Consideration of the four ethics principles of beneficence, non-maleficence, justice and autonomy will be part of this.

9.12.4.1 Risk

The term 'risk' refers both to the probability of a harm resulting from an activity and to its magnitude. Risk often stands for the combined probabilities and magnitude of several potential harms, whether they be psychological, sociological or physiological in nature. It should be noted that even inactivity may be associated with some risk and that every intervention, however simple it may be, involves some degree of risk.

Risk includes the consequence of a breach of confidentiality and also risks to others, through the use of scarce resources for research that might otherwise be used for patient care.

9.12.4.2 Considerations in risk assessment

In the process of risk assessment the following should be considered:²⁰

- 9.12.4.2.1** Risk identification is a qualitative description of the overall physical risks, the emotional or psychological hazards to the participant or his or her family, and the risks to which a participant or his or her family would not have been exposed had it not been for participation in the research project. Special care should be exercised in risk identification in vulnerable population groups, because some individuals are already exposed to such a degree of risk that it would be unacceptable to add to it the physical and emotional risks of being a research participant.²⁰ Although excluding such populations from the potential benefits of research may seem inappropriate, added protection must be afforded these groups to ensure a just distribution of risks as well. It must be shown why it is necessary to study a particular vulnerable group.²¹ Institutionalised individuals should be research participants only if the research is related to problems associated with institutionalised individuals.²¹
- 9.12.4.2.2** Risk estimation is a description of the probability or relative magnitude of harm.²⁰
- 9.12.4.2.3** Risk evaluation is the process of combining the results of risk identification and estimation with the perceptions of those involved. The perception of a risk formed by the participant or the participant's proxy is of overriding importance compared with the investigator's perception of the risk.²⁰

9.12.4.3 Categories of risk

The definitions of the various categories of risk vary in different countries.²⁰ The MRC agrees with many of the recommendations cited, 1-9 but for the sake of clarity these recommendations are summarised and modified as follows:

9.12.4.3.1 Negligible risk (*The smallest possible risk*)

In some procedures, studies or experiments, the risk is so small that it may be ignored. This is sometimes equated with the sort of risk accepted in everyday life.⁵ In reality, however, this equation is meaningless because of the wide range in the risks of daily life for different members of the population. The only alternative is to accept the idea that negligible risk is relative to the risk to which a person is already exposed. The higher the risk to which a person is already exposed, the higher the level of risk in a research procedure on that person which can be neglected. Such an idea is intolerable.²⁰

The MRC therefore defines 'negligible risk' as equal to the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives of people in a stable society or in the routine performance of physical or psychological examination or test.

Examples of negligible risks include simple physiological experiments involving exercise on healthy volunteers, procedures such as collecting urine by normal voiding, taking measurements of weight and height, collection of nail clippings or small samples of hair, developmental assessment, routine physical examination, observation of behaviour or changes of diet, or obtaining a single peripheral venous blood sample from an adult or bigger child.

9.12.4.3.2 Minimal risk

In more complex or invasive physiological and pharmacological studies it is helpful to consider not only the seriousness of an adverse effect that might result from a procedure, but also the probability of it happening. Therefore the term 'minimal risk' is used to cover two types of situations. The first is where there is a small chance of a recognised reaction which is in itself trivial, such as a mild headache or a feeling of lethargy. The second is where there is a very remote chance of serious injury or death, comparable, for example, to the risk of flying as a passenger on a scheduled aircraft.

An example of minimal risk includes obtaining a single peripheral venous blood sample, say up to 10 ml at a limb site, from a younger child by a competent veneselector, provided that the amount of blood collected is not excessive for the size of the child, and that the risks to which a child is exposed before entry into a research project are considered.

9.12.4.3.3 More than minimal risk

Examples of more than minimal risk might include procedures such as spinal taps, biopsies, certain drug tests and interventions that may entail hospitalisation, and behavioural interventions likely to cause psychological stress.²¹ Also included is the situation in which a procedure is of minimal risk but the outcome of that procedure is not. For example, venesection for an HIV test is of minimal risk, but a positive result represents more than minimal risk for an individual.

9.12.4.4 Risks in therapeutic and non-therapeutic research

9.12.4.4.1 In therapeutic research, the benefits likely to accrue to a participant should outweigh the risk of harm.⁷ As a general rule, research involving patients should not incur risk greater than minimal. An exception to this rule is where there is great potential benefit to the individual.

9.12.4.4.2 In non-therapeutic research the healthy volunteer may be subjected to no more than minimal risk as a result of participation.^{6,7} The possibility or probability that a particular investigation will be of benefit to humanity or to posterity, affords no defence in the event of legal proceedings.⁷ Incompetent participants in research should not be subjected to more than negligible risk.

9.12.4.5 Benefit

A benefit is the opposite of a harm, and refers to any favourable outcome of the research to society or to the individual. The outcome of research is never certain at the outset, and it is thus proper to consider the probability of benefit as well as its magnitude. In practice, 'benefit' often stands for the combined probabilities and magnitudes of several possible favourable outcomes.

9.12.4.5.1 The difference is recognised between therapeutic and non-therapeutic research in the context of risk/benefit analysis, and an individual's choice whether or not to participate in the research. In practice, however, the difference is seldom clear-cut. The same principles of risk limitation apply in therapeutic research as in non-therapeutic research. The requirement to inform the individual about what is proposed and to seek his or her consent, is the same in therapeutic research as in any other form of research involving persons.

9.12.4.6 Assessment of risk and benefit

9.12.4.6.1 The assessment of risk is an inexact science even when applied to conventional investigations and well-established treatments.²⁰ Research protocols provided to Research Ethics Committees must include estimates of the frequency and nature of complications associated with intended procedures and treatments, and this information should be contained in the participant information sheet.

9.12.4.6.2 Despite the lack of precision inherent in risk/benefit analysis when applied to research in humans, it is quite often a straightforward matter for a Research Ethics Committee to reach a conclusion that the risk is, or is not, reasonable in a particular case.

9.12.4.6.3 The risks of discomfort or other physical effects, as well as less obvious effects such as the possibility of psychological disturbance, breach of confidentiality and even simple inconvenience, must all be considered.

9.12.4.6.4 Committees should not rely solely on the view of the investigator when assessing the probability or the magnitude of harm. Independent expert opinion should be obtained whenever deemed necessary.

9.12.4.7 Reducing risk

Research Ethics Committees and investigators have a duty, before embarking on a risk/benefit analysis, to ensure that the risks inherent in the proposed research have been reduced to the minimum necessary to achieve the research objective. This duty includes consideration of whether alternative methods of obtaining the research information are available, consideration of whether lower risks might prevail in a different group of participants and whether participation by humans is required at all.

It is sensible for an investigator to discuss possible risks or benefits in a study with a member of a Research Ethics Committee before submitting an application.

9.12.4.8 Risk/benefit analysis and the individual

9.12.4.8.1 As well as taking steps to reduce the risk in research activities to the minimum, investigators should ensure that the study protocol effectively excludes special groups of people in whom the risk of participation would be particularly great, such as women of child-bearing potential in early trials of novel drugs.

9.12.4.8.2 Persons who consent to participate in a research project should have been given enough information to make their own choice. The concept of risk/benefit analysis should be conveyed as part of the procedure of seeking consent. The person's own assessment of risk and harm is sometimes more relevant to himself or herself than that of the expert. (See also 5.3.2.)

9.12.4.9 Outcome of risk/benefit analysis

9.12.4.9.1 The Research Ethics Committee needs to do more than a mere risk/benefit analysis in deciding whether research is justifiable. A proper assessment of whether the risk to a person is outweighed by the probable benefits, can be arrived at only if the Research Ethics Committee itself has a proper regard for the comfort and safety of the individual participant in terms of the principles of beneficence, non-maleficence, autonomy and justice. There is no easy method of defining the value to be put on comfort and safety, and a useful guide is probably whether or not members of the Committee would consent to participate in the research if they or members of their families were eligible to do so.

9.12.4.9.2 Whatever the perceived benefits, inhumane or careless treatment of participants is never justified.

9.13 Financial transactions and inducements

9.13.1 Inducements to healthy volunteers

There is a long tradition that both investigators and healthy volunteers in research are motivated by the desire to advance knowledge and help society. This spirit of altruism is to be admired and encouraged. However, many studies, particularly in pharmacology, are lengthy and tedious. It is reasonable that volunteers in this type of research should be paid, over and above reimbursement of expenses incurred. These payments are for inconvenience or discomfort.

Payments should never be for undergoing risk. Payments should not be to persuade people to volunteer against their better judgement or to induce them to volunteer more frequently than is advisable for their own good.

All payments to volunteers should be declared to and approved by the Research Ethics Committee.⁴ There is no absolute amount that can be defined, but what is reasonable is to provide transport and a meal at each session.

9.13.2 Inducements directed towards patients

Patients volunteer to take part in research for several reasons. A desire to help themselves is probably the commonest reason. Sometimes there is no likelihood of benefit to the individual patient. In this case the major motive may be a desire to help others who may have the disease, or mankind. Research Ethics Committees have a responsibility to ensure that patients are not 'used' in research and then abandoned.

9.13.2.1 Offer of otherwise unobtainable treatment

In the case of a new treatment which is known to offer important benefits to a patient when compared with other available treatments, but which is still in short supply, a requirement may be proposed that, in order to receive the treatment, the patient must consent to participation in research. Research Ethics Committees shall disapprove and discourage research projects that appear to take advantage of the strong desire of patients to receive the new treatment. This is

a potential problem area in developing countries in which resources are scarce.

9.13.2.2 Offer of superior care and attention

Although participation in research may sometimes bring benefits, such as those which may result from unusually detailed and careful supervision, improved care should not be offered as an inducement to participate.

9.13.2.3 Loyalty to the clinician

Undoubtedly, patients who like their clinicians and have confidence in them, are inclined to agree to proposals to take part in research. The reasons are probably many and complex. The patient must be assured, first, that he or she is completely free to decline to take part; second, that the refusal will be accepted without question and, third, that his or her care will then continue as if the matter had not arisen.

9.13.2.4 Patient's expenses

Where patients incur personal expense as a consequence of participation in research, it is proper that they should be reimbursed for that expenditure by the sponsor of the research.

9.13.2.5 Additional payments to patients

Payments are usually undesirable but are occasionally acceptable in studies which are lengthy and tedious. Payments should not be for undergoing risk. Payments should not be to persuade patients to volunteer against their better judgement. Small gifts given to child participants after completion of a research project should be allowed.²⁰ Any payments to be made should be declared to and scrutinised by the Research Ethics Committee. In deciding on what is a reasonable payment, a useful rule of thumb is to consider whether the payment will enrich a volunteer. There is no absolute amount that can be defined, but what is reasonable is to provide transport and a meal at each session.

9.13.3 Inducements directed towards investigators

9.13.3.1 Expenses

Where researchers incur personal expense as a direct consequence of undertaking research, it is quite proper for them to be reimbursed for that expenditure by the sponsor of the research.

9.13.3.2 Fees

Sponsors of research involving patients may properly engage clinicians to assist in that research, and it is proper for these clinicians to be paid a fee for their services. It is inappropriate that a clinician should be paid a fee for carrying out research work in sessions for which he or she is already being paid from another source. Sponsorship must be declared in the participant information sheet.

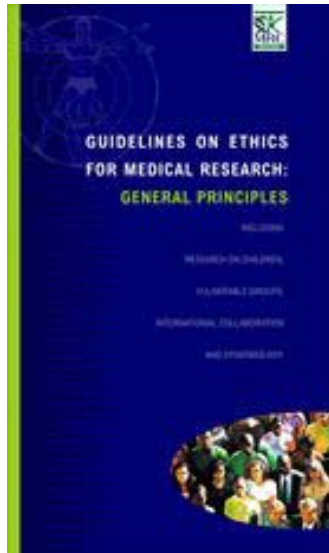
Ethical aspects of financial conflicts of interest in research have recently been addressed in some detail.^{22,23}

9.13.3.3 Contracts, payments and the responsibility of investigators

- 9.13.3.3.1** Investigators, pharmaceutical companies and ultimately patients have much to benefit from the close co-operation of clinicians with the officers of pharmaceutical companies in research projects and clinical trials of drugs. In providing opinions and services to companies, the principles of GCP^{9,10} must prevail.

9.13.3.4 *Payment for recruitment of patients into clinical trials*

All financial arrangements and payments to investigators should be divulged to Research Ethics Committees and, in the case of employees, to the employing authority. The total company budget for a clinical trial does not have to be declared.



10. Monitoring the conduct of research

10.1 National ethics body

Ideally, there should be a national ethics body to monitor Research Ethics Committees which should possess powers to sanction investigators who deviate from ethical standards in their research. Ideally too, the various professional councils of South Africa should consider health research in the same way that they consider any other activity of investigators, and discipline registered health professionals who have been found guilty of professional misconduct because of improper financial arrangements and scientific misconduct, for instance.

In addition to these influences on the investigator, there are the constraints provided by law. For example, any procedure carried out on a person without consent may be construed as an assault. In addition, delictual liability may ensue from treatment without informed consent.

10.2 Particular role of the Research Ethics Committee

10.2.1 Proposed research

10.2.1.1 The Research Ethics Committee probably achieves its principal influence merely by its existence. The knowledge that it is necessary to present an account of the intended research to an independent body, including professional peers and lay people, and of the concern that the Committee has for the interest of the participants, exerts a major controlling influence on the design of the study from the outset. The ethos of the Committee should be to help, not hinder investigators.

10.2.1.2 Ways in which the Committee can increase its influence when this seems necessary include:

- i. interviewing investigators in person;
- ii. sanctioning a limited pilot study with the requirement that the experience gained should be reported to the Committee before more extensive approval is given;
- iii. insistence that the investigator should submit the Participant Information Sheet for approval by the Committee, in order to exert greater influence over the extent and quality of the information made available to participants;
- iv. scrutiny by Research Ethics Committees of the Consent Form that will be used in order to ensure that participants are given adequate information before giving their consent.

10.3 Research in progress

Research Ethics Committee responsibilities continue while research is in progress.

10.4 Ownership of results of research

10.4.1 Intellectual property rights

- 10.4.1.1** For the purposes of this section the term Intellectual Property Rights (IPR) shall mean provisional patent applications, granted patents, trade marks, copyright, inventions, design rights (registered and unregistered), expertise, know-how, confidential information and all other intellectual property rights of whatever nature anywhere in the world.
- 10.4.1.2** It is the policy of the MRC that all IPR which result from funding provided by the MRC should be fully developed and made available to the public as a whole. For this to occur, investigators and inventors should disclose to the MRC all research results which, in their opinion, may amount to IPR in order to allow the MRC to decide whether it wishes to protect and commercialise that IPR.
- 10.4.1.3** It is also MRC policy that all investigators and inventors who have developed IPR should assign that IPR to the MRC if requested to do so, and sign all necessary documentation to effect transfer.
- 10.4.1.4** In the South African Medical Research Council Act, No 58 of 1991, Section 16 states that the rights in all inventions and in all improvements in respect of processes, apparatus, machines made by employees of the MRC, persons assisting the MRC with any investigation or research, and persons who are in receipt of MRC bursaries or grants-in-aid, automatically vest in the MRC unless otherwise agreed to by the MRC Board. Most educational institutions have put in place intellectual property policies which state that all IPR developed by their investigators belong to the educational institution. It should also be noted that the MRC has entered into agreement with a number of educational institutions, providing for the joint ownership of IPR and for sharing the proceeds of commercialisation of those rights.
- 10.4.1.5** Part of the proceeds from the commercialisation of IPR which originate from MRC-funded research should be used for the advancement of MRC research. The MRC has a royalty sharing scheme which states that these proceeds shall be shared as follows: one third to the investigator or inventor, one third to the MRC Centre/Unit/Group (if applicable) and one third to the MRC technology transfer office.
- 10.4.1.6** Investigators should not enter into material transfer agreements or confidentiality agreements without the prior consent of the MRC, as these agreements potentially have a bearing on the ability of the MRC to commercialise IPR.
- 10.4.1.7** In the event that the MRC carries out research on behalf of another person, government or administration, the IPR deriving from that research shall belong to the MRC unless it is otherwise agreed.

10.4.1.8 In most cases, industrial sponsors will not spend the time and effort required to get a product to the marketplace, without assurance of a monopoly and formal protection under IPR. Publication of certain technical information may destroy its commercial value and prevent formal protection under IPR. However, it is part of the function of the MRC to disseminate information and make it available to the public. Investigators should therefore reach prior agreements with industrial sponsors, allowing for the publication of research results after a short delay that will allow the sponsor to study (and possibly modify) the proposed disclosure, and to ensure that it will not result in the loss of IPR. Research Ethics Committees have a duty to ensure that research involving patients is conducted in an atmosphere which is as free as possible from commercial bias, and they should not approve proposals in which industrial sponsors seek to impose more restrictive conditions than the above, on the publication of research results.

10.4.1.9 The MRC may apply for a patent as assignee of an invention under the Patents Act, No 57 of 1978, or apply for a design as assignee of the design under the Designs Act, No 195 of 1993. In terms of the Copyright Act, No 98 of 1978, the author of an original work is the owner of the copyright in that work, unless the work was created by an employee during the course and scope of employment, in which case it belongs to the employer. The MRC has an intellectual property policy which states that copyright in all original works created by persons employed or funded by the MRC, belongs to the MRC. The MRC may assign the copyright in a work back to its creator if it feels that there is no commercial value attached to that copyright.

10.5 Research results

10.5.1 Responsibilities of investigators

Investigators have responsibilities to share possible benefits of research results with participants.

10.5.2 Rights of participants to results of research

In studies that involve sustained co-operation on the part of participants, it is good practice to make arrangements to inform them of the outcome of the research, in broad terms, and to combine this with a letter of thanks or a small gift in the case of children.

The benefits of research are to be made available to the research population and the local communities from which they were drawn, and adequate reports of the research must be made publicly accessible within a reasonable period of time.

All research participants should be informed of the outcome of the research in which they were involved.

Where communities or groups within a society are researched, they should be told the results of the study - for example, on hereditary diseases prevalent within their group. The participants have a right to be informed of new findings that may affect their rights, and they have a right to direct access to their original clinical records. (Refer to the provisions of the Promotion of Access to Information Act, No 2 of 2000, which applies to public bodies such as the MRC, for example. Patients have this right except where, in the view of the clinician practitioner concerned, disclosure is likely to cause serious harm to their physical or mental health or well-being, in which case proper counselling should be given.)

10.5.3 Should research results form part of hospital or clinical practice records?

Information that emerges in the course of research and is likely to assist the diagnosis or treatment of the participating patient, should be made available without delay to the clinician having overall responsibility for the patient's care. There is no need for all results of research investigations to be recorded in hospital or clinical practice records.

10.5.4 Disposal or continued storage of identifiable results

When the research is complete, the need for continued security and confidentiality remains.

10.6 Legal implications and arrangements for compensation (See Appendix IV for compensation guidelines.)

10.6.1 Introduction

The risk of injury, whether physical or psychological, occurring as a result of participation in research is generally low, but cannot be completely eliminated. Whatever the motives of the participant in agreeing to take part in research, there is an element of benefit to society, and it seems fair that society should bear some of the risk in financial terms. The participant's expectation that injury will be compensated is reasonable, and we believe that it has public support. It is recommended that investigators or sponsors of research take out professional indemnity insurance to cover themselves against eventual liability for claims arising from research activities.

10.6.2 Arrangements for compensation

10.6.2.1 Where the research involves invasive procedures or exposure to drugs or other products, there is a real risk of injury. Formal arrangements for compensation are necessary.

10.6.2.2 In the event of significant injury, the participant should be entitled to receive compensation regardless of whether or not there was negligence or legal liability on any other basis. The spirit of the guidelines of the Association of the British Pharmaceutical Industry (Appendix IV), should be followed. These are fair, no-blame compensation guidelines that do not infringe upon the legal rights of research participants.

10.7 Publication and authorship²⁴⁻³⁰

10.7.1 Introduction

Those engaged in research have a moral obligation to share their findings with other investigators, clinicians and society, for the mutual benefit of all. There are personal pressures on investigators to publish, and institutions in South Africa also benefit from the volume and quality of their research output.

Essential requirements for publication are that the research has been ethical from the beginning, through an institution's Research Ethics Committee review of the protocol, that results have been honestly gathered and reported and that due credit has been given to collaborators. Research results are usually published in scientific journals after peer review. In this process, reviewers appointed by an editor judge the quality of the research and the conclusions reached.

Ethical conduct in publishing is a mutual responsibility of authors and their parent institutions, of editors and of journal publishers.

10.7.2 Authors

Authorship of a paper should be settled as early as possible, the main criterion being public accountability for content of the paper. The assignment of authorship may cause problems. Loose assignment of authorship degrades the value of the effort put in by those who truly qualify as authors. Those who genuinely deserve authorship should not be deprived of it. Open communication among all the individuals involved in research is a guarantee of serving the best interests of all. The MRC endorses the recommendations of the International Committee of Medical Journal Editors,^{24,25} which are reproduced below.

10.7.2.1 Guidelines on authorship

10.7.2.1.1 International Committee of Medical Journal Editors^{24,25}

Each author should have participated sufficiently in the work to take public responsibility for the content. This participation must include:

- i. conception and design, or analysis and interpretation of data, or both;
- ii. drafting the article or revising it for critically important intellectual content;
- iii. final approval of the version to be published. Participation solely in the collection of data does not justify authorship. All elements of an article (i, ii and iii above) critical to its main conclusions, must be attributable to at least one author. A paper with corporate (collective) authorship must specify the key person responsible for the article; others contributing to the work should be recognised separately. Editors may require authors to justify the assignment of authorship.

10.7.2.1.2 Acknowledgements of intellectual contributions that fall short of authorship^{24,25}

At an appropriate place in the article (title page, footnote, or appendix to the text, as required by the relevant journal) one or more statements should specify:

- i. contributions that need acknowledgement but do not justify authorship; such as 'advice', 'critical review of study proposal', 'data collection', 'participation in clinical trial'. Such persons must have given their permission to be named;
- ii. acknowledgements of technical help;
- iii. acknowledgements of financial and material support;
- iv. financial relationships that might lead to a conflict of interests.

10.7.2.1.3 Information to be included in the covering letter^{24,25}

Manuscripts must be accompanied by a covering letter. The covering letter must include:

- i. information on prior duplicate publication or submission elsewhere of any part of the work;²⁴
- ii. a statement of financial or other relationships that might lead to a conflict of interests;
- iii. a statement that the manuscript has been read and approved by all authors;
- iv. the name, address, and telephone number of the corresponding author, who is responsible for communicating with the other authors about revisions and final approval of the proofs;
- v. a clear statement regarding the ethics approval of the research including the ethics clearance number.

The manuscript must be accompanied by copies of any permission to reproduce published material, to use illustrations of identifiable persons, or to name persons for their contributions.

10.7.2.1.4 Other guidelines

Data reported must be factual, not plagiarised, altered or selective. It should be published in as concise a form as possible, without repetition in several journals (multiple publication) or subdivision into multiple small units ('salami' publication). Where others' work is quoted, credit must be given through reference to the parent work. Unsubstantiated or exaggerated claims must be avoided. Release of research findings should be via professional biomedical journals, not non-refereed 'lay' publications, in order to avoid misleading sensationalism.²⁸

Anonymity of research participants and confidentiality of their details must be maintained. Any proprietary interest in a drug, treatment or institution must be clearly divulged.

It is a responsibility of each research team head to ensure that no fraudulent publications emanate from the team. Should fraudulent publication occur the responsibility is shared by all the authors.

10.7.3 Editors, peer reviewers and publishers

10.7.3.1 Editors have an obligation to treat all contributors equally and fairly. They have a responsibility to inform contributors of editorial policy (for example, via 'Instructions to Authors') as well as of reasons for rejection of articles.^{29,30} Acceptance or rejection of articles should be on scientific grounds only. Clearly prejudiced or politically biased reviewers' reports should be ignored, and the future use of such reviewers evaluated. Editors also have a responsibility to obtain a clear statement on ethics clearance of research submitted for publication, and to include this statement in the published work.

10.7.3.2 If fraud is suspected, it must be speedily and vigorously investigated and authors' home institutions and funding bodies informed. If fraud is proven, this must be openly recorded and previous work questioned.

10.7.3.3 Peer reviewers must respect and maintain the confidentiality of the unpublished information to which they have privileged access. There must be no theft of data, no plagiarism or deliberate delay in evaluation. Personal prejudices or bias must not be allowed to influence acceptance or rejection of articles. Reports to editors should be clear and professional. Where possible, suggestions should be made to improve the chances of publication of an article. Should a reviewer feel uncomfortable about evaluating a manuscript because of personal beliefs, the manuscript should be returned promptly to the editor, without review.

10.7.3.4 Journal publishers should ensure that their publications conform to the highest ethical standards, and should support editors' attempts to maintain these standards.

10.7.4 Ownership of data

Current opinion is that the sponsoring or employing institution owns the data and must hold the original data, should an investigator leave, so that the data are available for scrutiny. These should be kept for a minimum of five years after publication of an article. Copies of all data may be taken by the researcher with the permission of the sponsoring institution.

10.8 Liaison with the public media

This section is included for the benefit of MRC-supported investigators and it serves as a guideline for correct procedures rather than ethical practices.

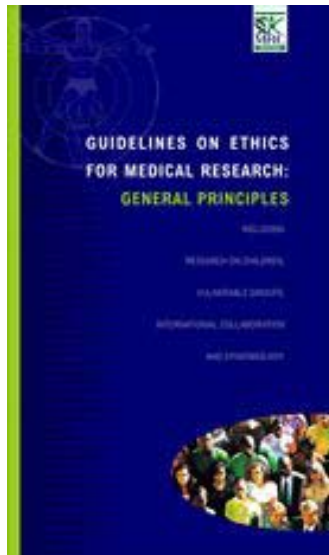
The MRC maintains responsible co-operation with all public news media in order to

communicate scientific information and to cultivate understanding and appreciation of MRC activities and of clinical research in general.

It is expected that Directors of MRC-supported units or centres, and short-term investigators who are supported by the MRC, should co-operate with the media at all times and to the best of their ability, for the sake of clinical research. Non-MRC personnel should be careful to follow procedures laid down within their host institutions, whereas MRC personnel may liaise with the public news media only with the permission of the President of the MRC or the President's nominee.

Cognisance should be taken of the 'Ingelfinger rule' when reporting research results: clinical research should not be reported in the scientific or lay press prior to publication in an appropriate peer-reviewed journal.²⁸

The Corporate Communication Division at Head Office is available to any MRC staff member or any affiliated researcher for advice and guidance regarding contact with the media. They have produced communication guidelines, Communication Guidelines of the Medical Research Council, 2001, which are available on the MRC's Internet under 'Corporate information'. Those without access to this Internet may request copies from leverne.getting@mrc.ac.za.



11. International collaborative research

11.1 Concerns

As globalisation increases, so does collaborative research. Concerns have been expressed about the ethics of this, particularly of clinical research in developing countries¹¹ and the application of standards of one country in another.³¹ Coupled to this are the intellectual property rights (IPR) of indigenous peoples (see also 10.5).

11.2 Ethics principles

In international collaborative research, as in any other research, the four principles of ethics apply. These are autonomy, beneficence, non-maleficence, and justice.

11.3 Collaborators

Those taking part in international collaborative research are host country institutions, collaborating country institutions, researchers from both, research participants and their communities.

11.3.1 Prior agreements

Before submission of a collaborative research proposal to a Research Ethics Committee, there shall be clear agreements on all aspects of the research. These include intellectual property sharing, management of the research process, division of responsibilities, finances, spreading of benefits and burdens, and any other appropriate aspects.

11.4 Principles

11.4.1 Commencement of research

- i. No research shall be undertaken until Research Ethics Committees of all collaborating institutions have given ethics approval to the research.
 - o Before granting ethics approval, such a Research Ethics Committee shall consider whether the study findings can, and will, be incorporated into the local healthcare system.³²
- ii. No research shall be undertaken after ethics approval of a protocol by a Research Ethics Committee until there is proper informed consent from participants, their families and communities according to local customs. This consent shall:
 - o be obtained in a manner that can be understood by the participants;
 - o include full disclosure of the aims and methods of the study, benefits and risks, confidentiality methods and commercial implications;
 - o be in written or taped form.

11.4.2 Exploitation

- i. There shall be no exploitation of one institution by another, nor of any investigator, research participant or community.
- ii. Intellectual property rights of institutions, investigators, participants and communities shall be respected, shared and acknowledged according to clear agreements before commencement of research.
- iii. There shall be equitable compensation of institutions, investigators, participants and communities. This shall be beyond pure financial compensation.
- iv. Institutions and investigators have a moral obligation to assist indigenous peoples, traditional societies and local communities to protect their knowledge and resources.
- v. Institutions and investigators have a moral obligation to respect what is sacred and secret by tradition.
- vi. No research shall be performed in a host country without local research collaboration in the design and conduct of that research.

11.4.3 Justification

- i. There must be clear justification of why research is done in a particular country, a particular institution, with a particular investigator, with a particular participant and in a particular community.
- ii. Unless there are compelling and acceptable reasons, no research shall be done in a host country that could just as easily be done in a collaborating country.
- iii. There must be clear potential benefit to the community being researched.
- iv. Those who are involved in international research should have some understanding of, and be sensitive to, the social, economic, and political milieu in which the research is taking place. This will include protection for research participants who are subject to systematic deprivations through poverty and other threats to freedom.³²

11.4.4 Benefit to host country

- i. No research shall commence without agreement between the host research institution and the collaborating institution. In this agreement the development of infrastructure and research capacity in the host country should be addressed.
- ii. Coercion and inducement of research participants is unacceptable.
- iii. There should be benefit - other than pure financial gain - to a host country community in which research is undertaken, such as access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
- iv. There must be a clear and fair system of compensation for research injury with clear lines of responsibility and guidelines on how to obtain this. GCP Guidelines for South Africa¹⁰ give these.
- v. Research findings should be translated into components of accessible care in the community being researched.³²
- vi. Participants should be provided with care or treatment they would not normally obtain.³²
- vii. Care must be taken to ensure that existing disparities are not more deeply entrenched by inappropriate deflection of local human or material resources away from the healthcare system towards the research project.³²

11.4.5 General

A clear agreement on the conduct of the collaborative research must be in place before a study begins including data management and research outputs. Before research begins, particular attention should be paid to the following points.

- i. The fate of data must be agreed.
- ii. The fate of any research specimens must be agreed.
- iii. Publication strategy must be agreed.
- iv. An ombudsman to settle disputes should be acceptable to all parties.
- v. There should be agreement on the nature of all benefits and their distribution.

12. Ethics guidelines for epidemiology

Guidelines for epidemiology have been discussed for 25 years.³³⁻³⁷ These include guidelines for the selection of study purpose, design and methods, collection of data, interpretation of results and publication of results. However, it has not been common practice to subject studies to ethics review once the collection of data has begun. The great difficulty of ethics monitoring once a study has begun, is that many published transgressions of ethics occur once the data collection has started.

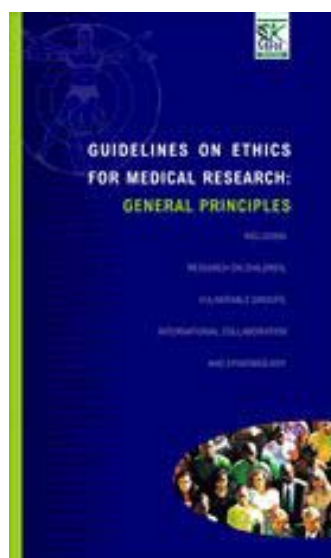
The American College of Epidemiology has listed 11 ethics guidelines for epidemiology that can be placed within the framework suggested by Soskolne:³⁸

1. The professional role of epidemiologists;
2. Minimising risks and protecting the welfare of research participants;
3. Providing benefits;
4. Ensuring an equitable distribution of risks and benefits;
5. Protecting confidentiality and privacy.
6. Obtaining the informed consent of participants:
 - o Elements of informed consent;
 - o Avoidance of manipulation and coercion;
 - o Conditions under which informed consent requirements might be waived.
7. Submitting proposed studies for ethical review;
8. Maintaining public trust:
 - o Adhering to the highest scientific standards;
 - o Involving community representatives in research.
9. Avoiding conflicts of interest and partiality;
10. Communicating ethical requirements to colleagues, employers, and sponsors and confronting unacceptable conduct;
11. Obligations to communities:
 - o Reporting results;
 - o Public health advocacy;
 - o Respecting cultural diversity.

12.1 'Public' versus 'health'

Resolution of ethical dilemmas in epidemiology revolves around notions of 'public' and 'health'. 'Public' has two categories: the individual as a member of society, and the public as a collective or community. 'Health' may be considered the presence or absence of disease or a continuum of the two. Epidemiology emphasises the individual in both definitions of 'public' and 'health'. However, public health decisions usually emphasise the community. The concern in broad policy decision-making is the trade-off between benefits to the community and risks to the individual.³⁹ Individuals typically fare less well than the community in prevention programs ('the prevention paradox').⁴⁰ In epidemiology, therefore, there is conflict between autonomy and distributive justice.

It is suggested that a practical approach to ethics in epidemiology would be to follow the general principles outlined in this book especially in Section 11.



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Recommended websites for more information

Australian National Health and Medical Research Council website with its numerous documents - <http://www.health.gov.au/nhmrc>

Canadian Tri-Council Policy Statement Ethical Conduct for Research Involving Humans - <http://www.mrc.gov.ca>

Office of Research Integrity - <http://www.ori.dhss.gov>

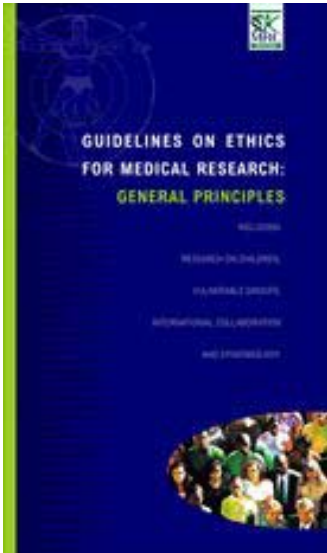
International Conference on Harmonisation - <http://www.mcclurenet.com/>

Appendix I: MRC checklist: quantitative research

The **MRC Ethics Committee** wishes to process applications for clearance as speedily as possible. To help us do this applicants need to provide a clear and comprehensive protocol for assessment.

Please note that all applications will be checked for completeness by the administration before submission to the Committee. All incomplete proposals will be returned to the applicant for updating which could result in unfortunate delays in the review process.

**Below is a checklist to help achieve this.
Please print, complete and attach the checklist to your submission**



- | | Yes | No |
|--|--------------------------|--------------------------|
| 1 Is the application labelled?
Give project title, National Programme. | <input type="checkbox"/> | <input type="checkbox"/> |
| 2 Are details of the investigators provided?
Name, title, FULL mailing address, telephone and fax numbers, e-mail address of principal investigator and co-investigators from each collaborating organisation. | <input type="checkbox"/> | <input type="checkbox"/> |
| 3 Have key words been given?
Up to 6 scientific descriptors (key words) for the project. | <input type="checkbox"/> | <input type="checkbox"/> |

4 **Is the following declaration provided, dated and signed?**

I, - ***name of principal investigator***- have read the MRC *Guidelines on Ethics for Medical Research* and have prepared this proposal with due cognisance of its content. Furthermore I will adhere to the principles expressed when conducting this proposed research project.

Did you have any difficulty with any specific provision in the guidelines concerning your proposal? If so, please provide details - this will be very helpful to the MRC Ethics Committee.

Please give a statement of the research problem.

5 **Has the application been approved by a project review committee?**
If YES, which one?

6 **Has the application been checked for content, grammar and spelling?**
If yes, by whom?

7 **Are the copies of the following attached?****[N/A = not applicable]**

Yes N/A

- An Executive Summary, stating the AIM, METHODS, OUTCOME and INTENDED FEEDBACK of the study.
- Subject information sheet
- Informed consent form

Are the technical terms in the above forms explained in lay terms?

- Translations into languages relevant to the study area. If yes, which language(s)?

If consent will be verbal or informed consent is not necessary, please explain why not

8 Is any questionnaire to be used provided?

9 Is confidentiality clarified?

10 Has consent from minors been explained?

If subjects are under age (less than 14 years for treatment or 18 years for an operation) from whom will consent be obtained, e.g. parent, guardian, etc.?

11 Has blood sampling been clarified?

Venous or arterial, the amount and frequency and by whom?

12 Has any drugs administration been specified?

If yes, have the drug, dose, frequency, and who will administer it been clarified?

13 Have drug side-effects been specified?

Yes No

14 Have the following protocol details been provided?

Table of Contents



Number the pages in the proposal and include page numbers in the contents.

Methodology details



- 1 Overall aim and specific objectives.
- 2 Background and rationale: This must be substantial and include references to or details of similar studies, and allow for thorough technical peer review by experts in your field.
- 3 Technical work plan: Describe in considerable detail your overall experimental design, methods and research protocols. Discuss research alternatives if your original assumptions/hypotheses prove incorrect.
- 4 Statistical planning: Has there been consultation with a statistician? If NO, please provide reasons. If YES, please give details including randomisation, sample size and proposed methods of analysis.
- 5 Time chart: Critical path analysis identifying when each activity is to take place. Identify points at which timing is critical (e.g. a season when a particular field study would need to be done).
- 6 References cited.
- 7 Description of methods applied.
- 8 Has this study been approved by the research group you operate in, or by any other peer group, for scientific validity?

If yes, name the group.

Management details



- 1 Management approach: Discuss the overall management of the project. Where is managerial responsibility? Consider specific functions such as reporting, financial management, procurement of equipment and research supplies, and management of field activities.
- 2 Staff and scientific collaboration: Who will do what, when and where? (one page).

- 3 Facilities: Describe the facilities and resources available for the proposed research.

Budget details



- 1 Budget: full detailed budget for each year. The following headings can act as a guide:
Salaries, equipment, its repair and maintenance, materials and supplies, training, consultation, travel, other, indirect costs/overheads.
- 2 Budget justification: Explain how the individual items of the budget were calculated. Justify major or unusual expenses.
- 3 Budget summary.
- 4 Has your research group reviewed and accepted the budget?
- 5 Do you believe the budget is fully sufficient to conduct the study ethically and scientifically?
- 6 Has the name of the sponsor of the study (if applicable) been indicated on the subject information sheet?

Details of researchers



CVs and publication lists of all senior personnel involved in the project.

NOTE: Only provide qualifications and scientific experience, e.g. publications, projects, presentations.

Other details

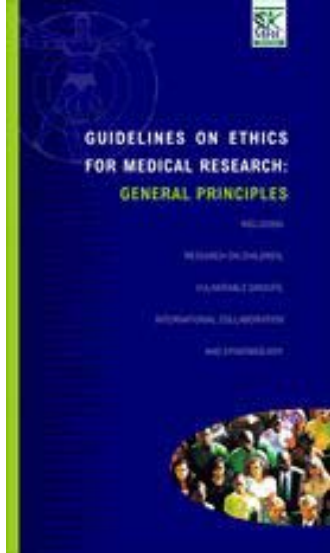


- 1 Ethical considerations: This must address all relevant ethical issues including: details of possible negative consequences to the study animals/subjects, information to be given to subjects, reporting back procedures to the community/authorities and an example of the consent form to be used.
- 2 Additional Review Bodies: does this protocol need to be reviewed by another institution or review board? If so, has it been submitted and what was the outcome? Please provide copies of relevant documentation.
- 3 Similar studies: Please list titles of any similar studies previously approved.

4 Please declare which of the following interests you may have in the study, such as:

- resources paid directly to you or your research account;
- potential financial benefits from the outcome of the study;
- direct financial interest in the company;
- any others;
- any gains to your family;
- travel sponsorship.

5 Name the possible (both positive and negative) short- and long-term consequences of the study.



Appendix II: MRC checklist: qualitative research

The **MRC Ethics Committee** wishes to process applications for clearance as speedily as possible. To help us do this applicants need to provide a clear and comprehensive protocol for assessment.

Please note that all applications will be checked for completeness by the administration before submission to the Committee. All incomplete proposals will be returned to the applicant for updating which could result in unfortunate delays in the review process.

**Below is a checklist to help achieve this.
Please print, complete and attach the checklist to your submission.**

- | | Yes | No |
|--|--------------------------|--------------------------|
| 1 Is the application labelled?
Give project title, National Programme. | <input type="checkbox"/> | <input type="checkbox"/> |
| 2 Are details of the investigators provided?
Name, title, FULL mailing address, telephone and fax numbers, e-mail address of principal investigator and co-investigators from each collaborating organisation. | <input type="checkbox"/> | <input type="checkbox"/> |
| 3 Have key words been given?
Up to 6 scientific descriptors (key words) for the project. | <input type="checkbox"/> | <input type="checkbox"/> |

4 **Is the following declaration provided, dated and signed?**

I, - ***name of principal investigator***- have read the MRC *Guidelines on Ethics for Medical Research* and have prepared this proposal with due cognisance of its content. Furthermore I will adhere to the principles expressed when conducting this proposed research project.

Did you have any difficulty with any specific provision in the guidelines concerning your proposal? If so, please provide details - this will be very helpful to the MRC Ethics Committee.

Please give a statement of the research problem.

5 **Has the application been approved by a project review committee?**
If YES, which one?

6 **Has the application been checked for content, grammar and spelling?**
If yes, by whom?

7 **Are the copies of the following attached?****[N/A = not applicable]**

Yes N/A

- An Executive Summary, stating the AIM, METHODS, OUTCOME and INTENDED FEEDBACK of the study.
- Subject information sheet
- Informed consent form

Are the technical terms in the above forms explained in lay terms?

- Translations into languages relevant to the study area. If yes, which language(s)?

If consent will be verbal or informed consent is not necessary, please explain why not

8 **Are questions that are going to be posed to participants provided?**

9 **Is confidentiality clarified?**

10 **Has consent from minors been explained?**

If subjects are under age (less than 14 years) from whom will consent be obtained?

11 **Have the following protocol details been provided?**

Table of Contents

Number the pages in the proposal and include page numbers in the contents.

Methodology details

- 1 Overall aim and specific objectives.
- 2 Background and rationale: This must be substantial and include references to or details of similar studies, and allow for thorough technical peer review by experts in your field.

- 3 Research work plan: Describe in considerable detail your overall research protocols. Discuss research alternatives if your original assumptions prove incorrect.
- 4 Data-analysis: purposive sampling, data saturation, method of analysis, independent coder.
- 5 Time chart: Critical path analysis identifying when each activity is to take place. Identify points at which timing is critical (e.g. a season when a particular field study would need to be done).
- 6 References cited.
- 7 Description of methods applied.
- 8 Has this study been approved by the research group you operate in, or by any other peer group, for scientific validity?

If yes, name the group.

Management details

- 1 Management approach: Discuss the overall management of the project. Where is managerial responsibility? Consider specific functions such as reporting, financial management, procurement of equipment and research supplies, and management of field activities.
- 2 Staff and scientific collaboration: Who will do what, when and where? (one page).
- 3 Facilities: Describe the facilities and resources available for the proposed research.

Budget details

- 1 Budget: full detailed budget for each year. The following headings can act as a guide:
Salaries, equipment, its repair and maintenance, materials and supplies, training, consultation, travel, other, indirect costs/overheads.
- 2 Budget justification: Explain how the individual items of the budget were calculated. Justify major or unusual expenses.

- 3 Budget summary.
- 4 Has your research group reviewed and accepted the budget?
- 5 Do you believe the budget is fully sufficient to conduct the study ethically and scientifically?
- 6 Has the name of the sponsor of the study (if applicable) been indicated on the subject information sheet?

Details of researchers

CVs and publication lists of all senior personnel involved in the project.

NOTE: Only provide qualifications and scientific experience, e.g. publications, projects, presentations.

Other details

- 1 Ethical considerations: This must address all relevant ethical issues including: details of possible negative consequences to the study animals/subjects, information to be given to subjects, reporting back procedures to the community/authorities and an example of the consent form to be used.
- 2 Additional Review Bodies: does this protocol need to be reviewed by another institution or review board? If so, has it been submitted and what was the outcome? Please provide copies of relevant documentation.
- 3 Similar studies: Please list titles of any similar studies previously approved.
- 4 Please declare which of the following interests you may have in the study, such as:

- resources paid directly to you or your research account;
- potential financial benefits from the outcome of the study;
- direct financial interest in the company;
- any others;
- any gains to your family;

- travel sponsorship.



5 Name the possible (both positive and negative) short- and long-term consequences of the study.

Appendix III: Sample information sheet

A user-friendly information sheet example

Some guidance on drawing up information sheets for human research projects

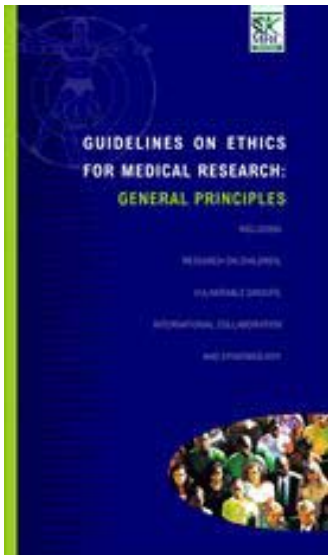
Information sheets to obtain consent from people to participate in a research study are essential. While their content will vary according to each study, general principles remain, so here are some tips to help you draw up your information sheet. It is a great help to imagine that you or your child are the potential research participants: what would you like to know? Write in a friendly tone, be open and honest, use simple language, ask for participation and all should be well.

1. As an introduction, greet the reader, say who you are and which institution you represent. Some useful greetings are: 'Hello', 'Dear Parent', 'Dear Clinic Staff', 'Dear Student', 'Dear Colleague'. It is unwise to use 'Dear Volunteer' when the reader has not yet been asked to volunteer.
2. Give a brief background or reason for the study. Explain why you have approached the potential research participant.
3. Explain what you would like to do, how often you need to do it, what specimens might be required, any compensation, payments or insurance, risks and benefits, discomforts, possible complications - then ask for participation.
4. Reassurance is necessary. Emphasise that participation in the study is completely voluntary, that one may decline (a softer word than refuse) to participate without penalty, that one may change one's mind later and withdraw from the study without any penalty or having to give reasons. Describe how confidentiality will be ensured, and explain what will be done if you find an abnormality. Take great care to reassure parents that no child will be forced to participate, even if a parent has given permission for participation. Remember that if children are able to understand what will be done, they must give assent as well. The parent should be the judge of the ability to understand.
5. Offer your intended participant the chance to obtain more information; for example, give the name and telephone number of a contact person. If there are any risks in your study, this is not optional - it must be done.
6. Be polite and friendly; do remember that everybody has freedom to participate - this is the principle of autonomy, a cornerstone of ethics.

Here is an example. It's not perfect; nothing ever is, but it should help.

Hello

We are scientists from the Medical Research Council and we are investigating the quality of



the food that Western Cape children eat. Do you think diet has any effect on school results? This is what we'd like to find out.

Why are we doing this? Research in developing countries in South America and Asia has shown that if energy and certain mineral intakes are low, children are sick more often, they miss school and their marks are not as good as they might be. We don't know if this is true in the Western Cape, so will be grateful if you and your children will participate in a study to examine this.

What do we expect from participants in the study? We think that if the amount of iron in the diet is increased slightly, minor illnesses such as colds and influenza may be less common. Your child's school has been selected because earlier studies there have shown that the iron intake of the children may be lower than it should be.

With the help of a biscuit company, we have developed a biscuit that is fortified (made healthier) with a little iron, but it looks and tastes just like the ordinary biscuit. We want to compare the effects of the two biscuits that taste exactly the same. One will contain some iron and the other will not. To do this, we will shuffle names of all participating children and place the names into two groups. One group will get the fortified biscuit and the other group will get the ordinary biscuit. Every school day for a full school year teachers will give out the biscuits, which will be in packets marked with the particular child's name. Only the people who packed the biscuits will know what is in each packet. What type of biscuit is being eaten by each particular child is recorded separately and this information will be kept secret until the very end of the study when the code will be broken. Records will be kept of attendance at school and of any illnesses.

In addition, we need to measure the iron levels in the blood of each participating child, before the study begins, and at the end. Nursing sisters will take one 5ml (1 teaspoon) sample at the two occasions provided that the child agrees. Sterile (free of germs), disposable equipment will be used once only, so there is no chance of any transfer of infection from one child to another. The technique is safe and there is only a slight prick as the needle is placed through the skin. To lessen the discomfort of this prick, a local anaesthetic ointment will be used on the skin. Over the years we have sampled blood from many thousands of children in this way without any problems.

May you withdraw your child from the study? Certainly, you may do this at any time without having to give a reason. Remember that the study is completely voluntary. Not taking part in it, or withdrawing from it, carries no adverse consequence of any sort - schooling will not be influenced. Your child will be asked to agree (assent) to take part in the study.

If you have any queries, more information may be obtained from Doctor AN Other at telephone number (021) 123-4567.

If you are happy to allow your child to take part in the study, please read and sign the attached consent form.

Thank you
Dr AN Other

Appendix IV: Clinical trial compensation guidelines

Clinical Trial Compensation Guidelines

Preamble

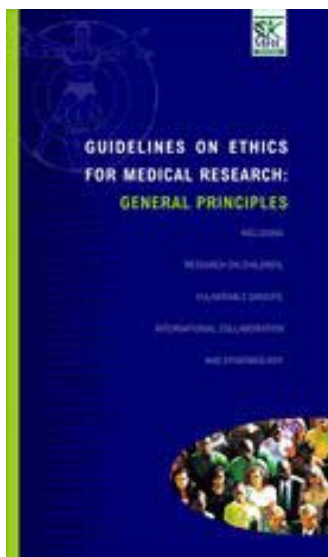
The Clinical Trials Committee of the South African Medicines Control Council has adopted the following guidelines on clinical trial compensation. These Guidelines are based on those of the Association of the British Pharmaceutical Industry.¹⁰

Introduction

The Association of the British Pharmaceutical Industry favours a simple and expeditious procedure in relation to the provision of compensation for injury caused by a participation in clinical trials. The Association therefore recommends that a member company sponsoring a clinical trial should provide without legal commitment a written assurance to the investigator - and through him/her to the relevant Research Ethics Committee - that the following Guidelines will be adhered to in the event of injury caused to a patient attributable to participation in the trial question.

1. Basic principles

- 1.1 Notwithstanding the absence of legal commitment, the company should pay compensation to patient-volunteers suffering bodily injury (including death) in accordance with these Guidelines.
- 1.2 Compensation should be paid when, on the balance of probabilities, the injury was attributable to the administration of a medicinal product under trial or any clinical intervention or procedure provided for by the protocol that would not have occurred but for the inclusion of the patient in the trial.
- 1.3 Compensation should be paid to a child injured in utero through the participation of the subject's mother in a clinical trial as if the child were patient-volunteer with the full benefits of these Guidelines.
- 1.4 Compensation should only be paid for the more serious injury of an enduring and disabling character (including exacerbation of an existing condition) and not for temporary pain or discomfort or less serious or curable complaints.
- 1.5 Where there is an adverse reaction to a medicinal product under trial and injury is caused by a procedure adopted to deal with that adverse reaction, compensation should be paid for such injury as if it were caused directly by the medicinal product under trial.



- 1.6 Neither the fact that the adverse reaction causing the injury was foreseeable or predictable, nor the fact that the patient has freely consented (whether in writing or otherwise) to participate in the trial should exclude patient from consideration for compensation under these Guidelines, although compensation may be abated or excluded in the light of the factors described in paragraph 4.2 below.
- 1.7 For the avoidance of doubt, compensation should be paid regardless of whether the patient is able to prove that the company has been negligent in relation to research or development of the medicinal product under trial or that the project is defective and therefore, as the producer, the company is subject to strict liability in respect of injuries caused by it.

2. Type of clinical research covered

- 2.1 These Guidelines apply to injury caused to patients involved in Phase II and Phase III trials, that is to say, patients under treatment and surveillance (usually in hospital) and suffering from the ailment which the medicinal product under trial is intended but for which a product licence does not exist or does not authorise supply for administration under the conditions of the trial.
- 2.2 These Guidelines do not apply to injuries arising from studies in non-patient volunteers (Phase I), whether or not they are in hospital, for which separate Guidelines for compensation already exist.¹
- 2.3 These guidelines do not apply to injury arising from clinical trials on marketed products (Phase IV) where a product licence exists authorising supply for administration under the conditions of the trial, except to the extent that the injury is caused to a patient as a direct result of procedures undertaken in accordance with the protocol (but not any product administered) to which the patient would not have been exposed had treatment been other than in the course of the trial.
- 2.4 These guidelines do not apply to clinical trials, which have not been initiated or directly sponsored by the company providing the product for research. When trials of products are initiated independently by doctors under the appropriate Medicines Act 1968 exemptions, responsibility for the health and welfare of patients rests with the doctor alone (see also paragraph 5.2 below).

3. Limitations

- 3.1 No compensation should be paid for the failure of the medicinal product to have its intended effect or to provide any other benefit to the patient.
- 3.2 No compensation should be paid for injury caused by other licensed medicinal products administered to the patient for the purpose of comparison with the product under trial.
- 3.3 No compensation should be paid to patients receiving placebo in consideration of its failure to provide a therapeutic benefit.

3.4 No compensation should be paid (or should be abated as the case may be) to the extent that the injury has arisen:

3.4.1 through a significant departure from the agreed protocol;

3.4.2 through the wrongful act or default of a third party, including a doctor's failure to deal adequately with an adverse reaction; or

3.4.3 through contributory negligence by the patient.

4. Assessment of compensation

4.1 The amount of compensation paid should be appropriate to the nature, severity and persistence of the injury and should in general terms be consistent with the quantum of damages commonly awarded for similar injuries by Court of law in cases where legal liability is admitted.

4.2 Compensation may be debated, when certain circumstances excluded, in the light of the following factors (on which will depend the level of risk the patient can reasonably be expected to accept):

4.2.1 the seriousness of the disease being treated, the degree of probability that adverse reactions will occur and any warnings given; or

4.2.2 the risks and benefits of established treatments relative to those known or suspected of the trial medicine.

This reflects the fact that flexibility is required given the particular patient's circumstances. As an extreme example, there may be a patient suffering from a serious or life-threatening disease who is warned of a certain defined risk of an adverse reaction. Participation in the trial is then based on an expectation that the benefit/risk ratio associated with participation may be better than that associated with alternative treatment. It is, therefore, reasonable that the patient accepts the high-risk and should not expect compensation for the occurrence of the adverse reaction of which he or she was told.

4.3 In any case where the company concedes that a payment should be made to a patient but there exists the difference of opinion between company and patient as to the appropriate level of compensation, it is recommended that the company agrees to seek at its own costs (and make available to the patient) the opinion of a mutually acceptable independent expert, and that his opinion should be given substantial weight by the company in reaching its decision on the appropriate payment to be made.

5. Miscellaneous

5.1 Claims pursuant to the Guidelines should be made by the patient to the company, preferably via the investigator, seeking out details of the nature and background of the claim and, subject to the patient providing on request an authority for the company to review any medical records relevant to the claim, the company should consider the claim expeditiously.

- 5.2** The undertaking given by a company extends to injury arising (at whatever time) from all administrations, clinical interventions or procedures occurring during the course of the trial but not to treatment extended beyond the end of the trial at the instigation of the investigator. The use of unlicensed products beyond the trial period is wholly the responsibility of the treating doctor and in this regard attention is drawn to the advice provided to doctors in MAL 302 concerning the desirability of doctors notifying their protection society of the use of unlicensed products.
- 5.3** The fact that company has agreed to abide by these Guidelines in respect of a trial does not affect the right of a patient to pursue a legal remedy in respect of injury alleged to have been suffered as a result of participation. Nonetheless, patients will normally be asked to accept that any payment made under the Guidelines will be in full settlement of their claims.
- 5.4** A company sponsoring a trial should encourage the investigator to make clear to participating patients that the trial is being conducted subject to the ABPI guidelines relating to compensation for injury arising in the course of clinical trials and have available copies of the Guidelines should they be requested.
- 5.5** Where studies are carried out in a hospital, the hospital continues to have a duty of care to the patient being treated within that hospital, whether or not the patient is participating in an MRC-supported study. Therefore the MRC does not accept liability for negligence on the part of employees of, or staff engaged by, hospitals. This applies whether the hospital is private or public sector. The MRC cannot be held liable for any breach in the hospital's duty of care.

6. References

1. Guidelines for medical experiments in non-patient human volunteers, ABPI March 1988, as amended May 1990.
2. MAL30 A guide to the provisions affecting doctors and dentists, DHSS, revised June 1985.

Appendix V: The Belmont Report

Office of the Secretary
Ethical Principles and Guidelines for the Protection of Human Subjects of Research
The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

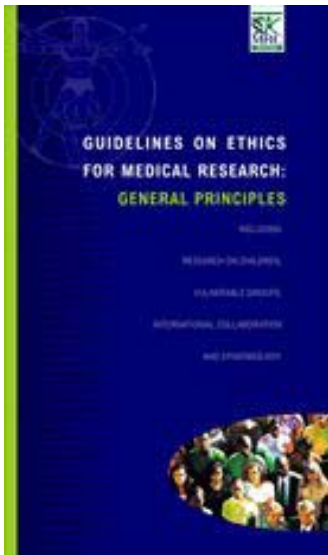
AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research and (iv) the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and



Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.
Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.
Robert E. Cooke, M.D., President, Medical College of Pennsylvania.
Dorothy I. Height, President, National Council of Negro Women, Inc.
Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.
Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.
Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.
***David W. Louisell, J.D., Professor of Law, University of California at Berkeley.
Donald W. Seldin, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas at Dallas.
***Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.
***Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.

***Deceased.

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes(1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand,

and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called 'experimental' when the terms 'experimental' and 'research' are not carefully defined.

For the most part, the term 'practice' refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.(2) By contrast, the term 'research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is 'experimental', in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.(3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression 'basic ethical principles' refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. **Respect for Persons.** Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated. Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to 'volunteer' or to 'protect' them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. **Beneficence.** Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term 'beneficence' is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

The Hippocratic maxim 'do no harm' has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients 'according to their best judgment'. Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give fore thought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children - even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. **Justice.** Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of 'fairness in distribution' or 'what is deserved'. An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940s, the Tuskegee syphilis study used disadvantaged rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g. welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice

demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. **Informed Consent.** Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be

withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be given to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g. infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence - especially where possible sanctions are involved - urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be

entitled.

2. **Assessment of Risks and Benefits.** The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term 'risk' refers to a possibility that harm may occur. However, when expressions such as 'small risk' or 'high risk' are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term 'benefit' is used in the research context to refer to something of positive value related to health or welfare. Unlike 'risk', 'benefit' is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal Regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be 'balanced' and shown to be 'in a favorable ratio'. The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research,

and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the presupposition of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimate of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. **Selection of Subjects.** Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only 'undesirable' persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g. adults before children) and that some classes of potential subjects (e.g. the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Appendix VI: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964
and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

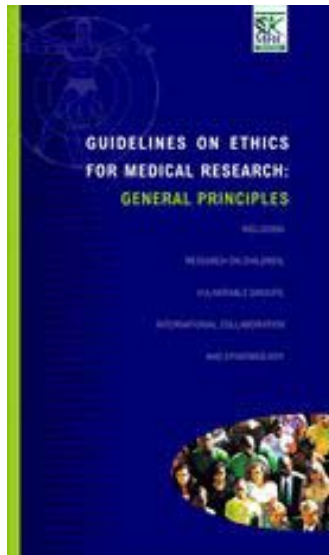
41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. Introduction.

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory



requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic principles for all medical research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interests and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom, it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional principles for medical research combined with medical care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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(Available at: http://www.wma.net/e/policy/17-c_e.html)

Appendix VII: The Nuremberg Code

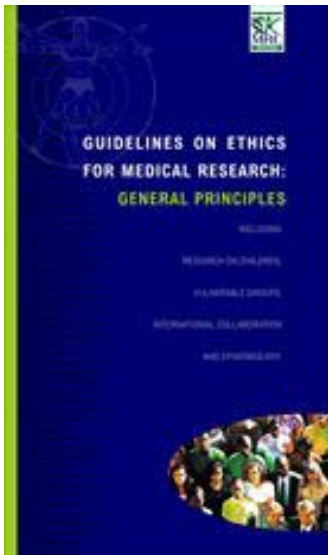
From "Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10", Vol. 2, Nuremberg, October 1946 - April 1949. (Washington, DC: US Government Printing Office, 1949). pp 181-182.

The great weight of the evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts.

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problems under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except perhaps, in those experiments where the experimental physicians also serve as subjects.



6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe in the exercise of the good faith, superior skill and careful judgement required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

(Available at: <http://ecco.bsee.swin.edu.au/studes/ethics/Nuremberg.html>)