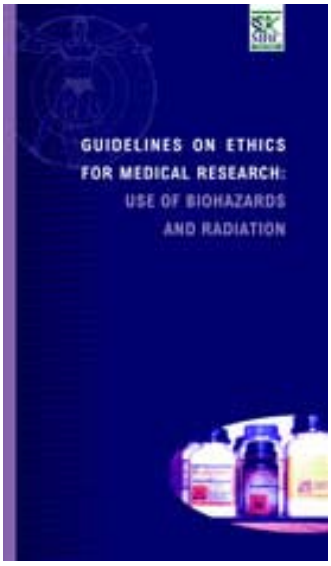
GUIDELINES ON ETHICS FOR MEDICAL RESEARCH:

USE OF BIOHAZARDS AND RADIATION



Book 4: Use of Biohazards and Radiation.

We extend our grateful thanks to the members of the current Editorial Committee and to colleagues who contributed to the third edition, on which the current edition is based. In the order that they appeared in the previous edition they are:

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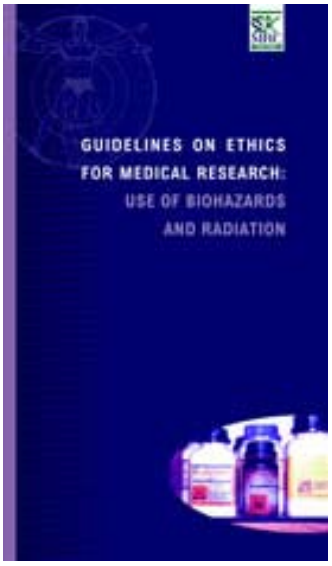


Book 4: Preface

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;
2. the Truth and Reconciliation Commission; and
3. a surge of interest world-wide in the field of bioethics, particularly as transgressions of ethics around the world have been exposed.
4. 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:
    - 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?
    - 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?

5. 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.

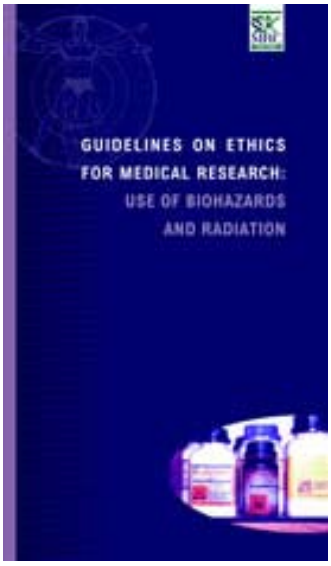
In conclusion:

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.
2. Ethics in developing countries continues to demystify and destroy the male liberal racial theory that emerged in the last century.
3. 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.
4. 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.
5. 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 4: 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.

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, in Book 1: *General Principles*) 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 Health*Info* website mentioned on page v) 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

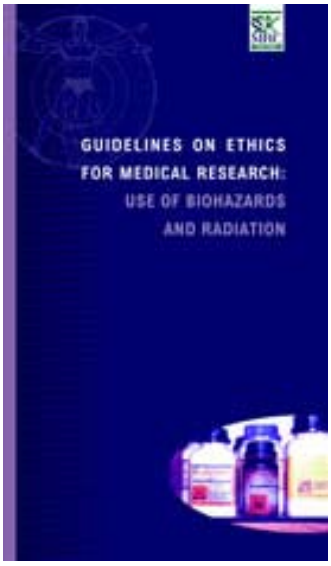
Guidelines on Ethics for Medical Research: Use of Animals in Research.

Book 4

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

Book 5

Guidelines on Ethics for Medical Research: HIV Vaccine Trials



Book 4: 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 4 of the series Guidelines on Ethics for Medical Research is extensively based on three previous editions and on international documents1-9 (see also Appendices V - VII, in Book 1) 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)

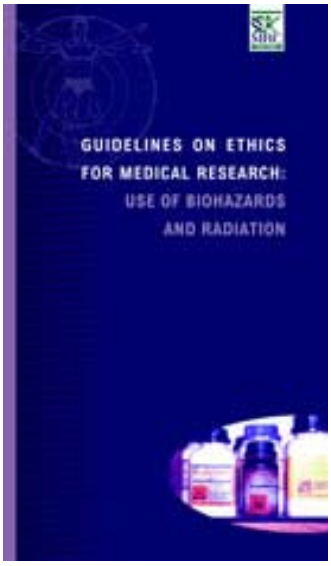
There is considerable debate about whether one or more of these principles require or deserve preference when ethical problems are considered. For example, the trend in most Western countries seems to emphasise autonomy over beneficence. This counters the alleged danger of paternalism in the practice 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 for a particular research project.



Book 4: General biohazards - an introducton

Biosafety is concerned with the containment methods required when managing parasites, infectious agents and infected or potentially infected animals, tissues or other materials, as well as radiation. Biological fluids such as blood, and even cell lines (particularly primary cell cultures), may harbour a variety of pathogenic organisms, such as HIV, hepatitis viruses or prions, and thus are a biohazard risk.

The purpose of biosafety is to reduce exposure of persons, animals and the outside environment to potentially hazardous agents. Unnecessary or avoidable exposure to such hazards is ethically unacceptable. Organisms have traditionally been classified according to their characteristics, such as pathogenicity, infectious dose required for disease, mode of transmission, hosts and availability of preventive measures and treatment. Although organisms have been classified according to risk groups in the past, it is arguably more appropriate to consider the handling and containment requirements, as outlined below.

Samples obtained, whether of prokaryotic origin or from human or animal subjects, must be obtained with the consent of the agency or subject, and the material is subject to the ethical and other considerations of the provider. Care must be exercised to prevent the importation of potentially biohazardous materials into a facility currently not involved with that material.

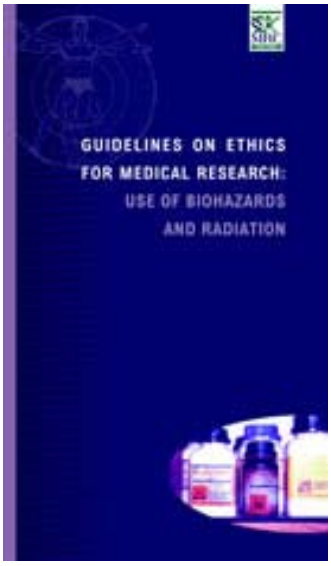
The Directorate: Genetic Resources of the National Department of Agriculture, Private Bag X973, Pretoria, 0001, must be consulted about pilot experiments, trials or the release into the environment of genetically modified organisms in South Africa, except where this involves only basic research in a contained environment.

Reasonable precautions must be taken with any work involving biological material or radiation. The difficulty lies in defining reasonable or absolute requirements. It is unlikely that we will be able to ensure a situation of no risk, as there may be unknown agents or effects still to be defined. It should be noted that the risk to, or exposure of, laboratory workers or researchers is often less than in the case of health care workers such as nurses or clinicians, who have regular and frequent contact with patients or body fluids harbouring a variety of infectious agents. In all cases however, one attempts to minimise exposure and risk.

The recommendations that follow apply essentially to immunocompetent individuals. Immunocompromised individuals are at increased risk and should be advised to avoid additional risk. Persons who believe they may be immunocompromised should inform their supervisory authority, and their case should be carefully considered before exposure occurs. In any deliberation, perhaps the most important safety consideration is 'distance'. Distance is not simply geographical location, but implies barriers, whether these are full-body protective clothing for avoidance of pathogenic organisms, or lead screens to confine radiation exposure.

In a broad context, work should not contravene other general ethical considerations, such as those approved in the MRC Guidelines on Ethics for Medical Research, the Declaration of Helsinki (**http://www.wma.net/e/policy/17-c_e.html**), the Cartagena Protocol on Biosafety or the Convention on Biological Diversity.

Detailed laboratory biosafety guidelines are beyond the scope of this document, but are available in publications dealing with various pathogens or from the Internet, such as the Canadian Guidelines (**http://www.hc-sc.gc.ca/pphb-dgspsp/ols-bsl/lbg-ldmbl/index.html**).



Book 4: Worker safety

All research protocols involving genetic manipulation should be considered by Research Ethics Committees and safety committees. Biosafety[10] is chiefly concerned with the biohazards that may result from manipulating harmful organisms. After thorough risk analysis, all relevant protocols should be designed to reduce hazards to laboratory workers and the environment. Workers must be adequately trained before embarking on any work, and the necessary containment facilities and equipment must be installed before permission will be granted in respect of the relevant biosafety levels of experiments.

It is the duty of the host institution to ensure that adequate facilities are present and that control is exercised over the researchers and workers who are to be involved. The host institution should have a committee, which may be a Research Ethics Committee, concerned with biosafety and containment, but not necessarily limited to such considerations. All relevant experiments to be conducted in the institution must be approved by this authority, which will be responsible for monitoring the procedures in the host institution.

Book 4: Risk assessment

Risk assessment is the activity concerned with the decision to approve activities associated with a biohazard. Apart from biohazards associated with any given organism, additional factors need to be considered. These may include, but not be limited to, the following:

i. the concentration and quantity (number) of organisms concerned;
2. the stability and viability of the organism;
3. the potential for transmission, whether by contact or aerosol;
4. the nature of the work envisaged (whether liquid culture or aerosol challenge);
5. specific risks associated with GMOs (genetically modified organisms);
6. risk of by-products, such as spores, toxins, virulence factors;
7. risk of unknown contaminants such as cells or cell lines with latent oncogenic viruses or other associated viruses.

Some considerations are listed below.

4.1 Prokaryotes (including microbes, viruses)

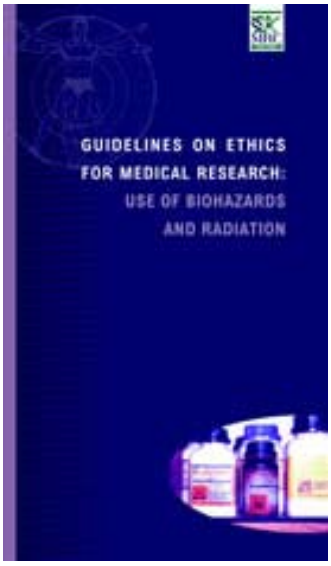
There is a wealth of knowledge concerning the pathogenic potential of most microbes and viruses. This information is readily available, even at textbook level.

4.2 Eukaryotes

a. Parasites: There is a considerable body of information concerning most parasites.

There may be different risks associated with parasites, depending on whether the project involves in vivo work (animal model) or in vitro (cultured) organisms. Furthermore, the risk may differ according to the stage of development. The host range is a further consideration for risk assessment.

2. Intact organisms: These may be pathogenic, such as protozoans, or they may pose handling risks in general, like venomous animals. Alternatively, the closer the organism is to humans phylogenetically, the greater the potential risk from zoonoses (see also (c) and (d) below).
3. Cells, cell lines or body fluids: Tissue samples or body fluids present high risks and should be treated with extreme care. The risk originates not from the cells themselves, but from their potential to harbour pathogenic organisms or agents, including prions. The risk is assessed at the level of the agent of highest possible risk. (d) Cultured material: There is a risk that cultured cells or tissue samples may contain pathogens, as in (b) and (c) above.



Book 4: Requirements

5.1 General

A summary of the main requirements relating to biological safety is given below. Each institute, centre, department or group carrying out biological work should make arrangements to:

i. set up or contact an appropriate committee, group or person to advise on biological safety measures to be taken in accordance with institutional guidance;
2. appoint a Biological Safety Officer - and deputy, if appropriate;
3. assess all work involving pathogens and, in the case of genetic modification, prepare a written assessment in accordance with the approved method;
4. ensure that the laboratory facilities conform to the required containment levels;
5. ensure the correct maintenance and testing of microbiological safety cabinets;
6. notify the Safety Officer in advance of the start of work involving Group 3 or 4 pathogens;
7. notify the Safety Officer before starting work involving genetic modification, certain uses of genetically modified organisms, the intentional release of genetically modified organisms, and any genetic modification work requiring containment level 3 or 4;
8. report micro-organisms used or intended to be used in the department;
9. report proposals to use microbiological safety cabinets that are vented to the outside air;
10. ensure that adequate training, instruction and supervision are provided;
11. report, on request, details of genetic modification work requiring containment levels 1 and 2.

Work undertaken may be assigned to different hazard groups with various containment requirements and attendant risk assessment. All work must be carried out in a facility with the correct containment level or higher. It is the responsibility of the supervisor or host institution to ensure that this is done. Codes of practice relating to the containment levels should be available. Alternatively, the researcher may refer to various national or international guidelines, such as University of Oxford Guideline S4/92.[10]

5.2 Biosafety

Four biosafety levels are defined and the required laboratory facilities must be available before the project is initiated. The selection of any given biosafety level depends on the risk assessment of the project.

5.2.1 Biosafety level 1 (BL1)

The standard laboratory practices, safety equipment and facilities appropriate for secondary educational and undergraduate training and teaching are required. Research involving defined and characterised strains of viable infectious agents not known to cause disease in

healthy adults or to colonise humans or animals falls into this category.

Requirements: A basic laboratory without safety equipment is adequate. Primary containment must be practised by adhering to standard laboratory practices during open bench operations.

5.2.2 Biosafety level 2 (BL2)
Risk is associated with exposure by ingestion, inoculation or mucous membrane contamination, but not normally by exposure to aerosols.

The standard microbiological practices plus the following are necessary: the wearing of protective gloves and coats when conducting procedures with infective agents; decontamination of all waste; the erection of biohazard signs; control of access. These precautions are applicable in clinical, diagnostic, teaching and other facilities when working with the broad spectrum of indigenous, moderate-risk agents present in the community and associated with human disease of varying severity. Activities with low aerosol potential using such agents may be conducted on the open bench, using good microbiological techniques.

Requirements: A containment laboratory with partial containment equipment (Class I or II biological safety cabinets) must be used to isolate mechanical and manipulative procedures that produce readily detectable aerosols. Sealed rotor centrifuges and an autoclave are required.

BL2 applies to an organism that may cause human disease and be a hazard to laboratory workers, but is unlikely to spread to the community. Laboratory exposure rarely produces infection and effective prophylaxis or effective treatment is usually available.

5.2.3 Biosafety level 3 (BL3)
Aerosol-borne disease is a primary concern at this level, which also implies high risk at low dosage of life-threatening disease.

In addition to BL2 practices, the following are necessary: special laboratory clothing and controlled access. These precautions are appropriate in clinical, diagnostic, teaching, research or production facilities when working with indigenous or exotic agents which may readily cause potentially fatal infections.

Requirements: A containment laboratory with partial or total containment equipment (Class I, II or III biological safety cabinets) must be used to isolate all procedures that may produce aerosols.

This includes the availability of respiratory protective equipment and air-conditioning; HEPA filtered exhaust air; controlled access and training of all users of the facility. Regular monitoring of users is suggested, and a medical consultant should be available for referral. Standard operating procedures (SOP) should be adhered to and there should be ready access to appropriate medical treatment - for example, access to anti-retrovirals in the case of needle-stick injuries when working with HIV-containing material.

BL3 applies to organisms that may cause severe human disease and that present a serious hazard to laboratory workers. It may present a risk of spreading to the community, but there is usually effective prophylaxis or treatment available.

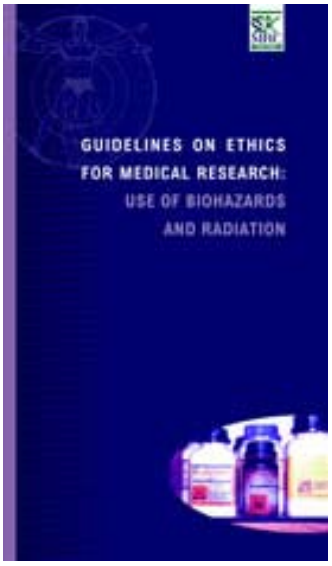
5.2.4 Biosafety level 4 (BL4)
In this case, agents are readily transmissible, they produce very serious and often fatal

disease and treatment is limited or unavailable. This category of biocontainment applies to work on parasites or infectious agents such as exotic or eradicated agents whose acquisition and maintenance is entirely proscribed or is authorised only in exceptional circumstances by the authorities in charge of health, agriculture and the environment. Access to such a facility should be severely restricted and closely monitored, and the unit should preferably be structurally independent. The unit must be sealed and airtight.

In addition to BL3 practices, the following are necessary: entrance through a changeroom where street clothing is removed and laboratory clothing donned; shower on exit; all wastes are decontaminated on exit from the facility.

Requirements: A maximum containment laboratory with total containment equipment (Class III biological safety cabinets) or full-body, air-supplied, positive-pressure, personnel suits for all procedures and activities. All effluents, including air, must be decontaminated.

BL4 applies to an organism that causes severe human disease and is a serious hazard to laboratory workers. It may present a high risk of spread to the community and there is usually no effective prophylaxis or treatment.



Book 4: Genetically modified organisms (GMOs) and related issues

The basic guidelines in this work are that maximum care be exercised in the interests of workers, human or animal subjects and research. The terms genetic modification, genetic manipulation, genetic engineering or recombinant DNA technology are interchangeable. These terms are usually defined to mean the propagation of heritable material by the insertion of that material, prepared by whatever means outside a cell or organism, into a cell or organism in which it does not occur naturally, either directly or into a vector system which is then incorporated into the cell or organism.

Considerable differences exist in the technology and techniques required to deal with prokaryotic or eukaryotic organisms used in genetic manipulation. Research utilising cultured organisms such as prokaryotic or eukaryotic single cells (with the exception of fertilised ova) may be regarded as ethically acceptable, provided the necessary containment facilities are used.

The application of this technology in animal research may be subdivided into various categories. The release of a recombinant organism or cell which may be cultured in vitro and then inserted either by DNA technology, as with the use of a virus, or by surgical means, in replacement of bone marrow cells, may be regarded as gene therapy by cell transplantation. This technology as applied in animals is ethically acceptable, provided the guidelines with regard to animal research are followed (see Book 3). The manipulation of genes in animal research must be limited by biohazard considerations. The manipulation of animal embryos or germ-line cells to create transgenic animals is ethically acceptable where the guidelines regarding animal research are followed.

A detailed discussion of recombinant agents is beyond the scope of this book. However, each case should be considered for risk potential. Many experiments involving recombination are done in non-pathogenic, disabled organisms and present no known risk, while others may present risk. Risk, in the case of GMOs, may involve the environment and containment may be required, although no direct risk to human or animal health is evident.

Risk may be assessed as a function of the following factors:

i. access: the risk that a micro-organism containing recombinant DNA sequences might infect a person or animal exposed to it;
2. expression: the risk that polypeptides coded for by the recombinant DNA could be produced or expressed by the organism;
3. damage: the risk that polypeptides expressed by the organism might damage the host.

The risk may be estimated in terms of the probability per unit micro-organism. A value of 1 means that all micro-organisms are expected to have access and to express a polypeptide that could cause some damage to the host. A value of 10 - 3 means that the likelihood of this occurring is 1 in 103 micro-organisms. The product of the three factors indicates the required category of containment.

Total risk factor	Containment
10^{-15} or less	Good microbiological practice
10^{-12} or less	Category 1
10^{-9} or less	Category 2
10^{-6} or less	Category 3
More than 10^{-6}	Category 4

Risk increases with large-scale growth, and extra containment may be required for a given organism.

Any GMO that is potentially viable as a free-living organism and is to be grown, cultured, propagated or used as a vaccine outside a contained environment, should be regarded as posing some risk unless assessed otherwise. Assessment is beyond the scope of this document and must be done by the relevant national authority, at present the GMO Advisory Committee or the Directorate: Genetic Resources, National Department of Agriculture. If the organism is approved, the Department will issue a permit for the work in terms of the GMO Act, No. 15 of 1997.

There are three different aspects of genetic engineering as applied directly to humans.

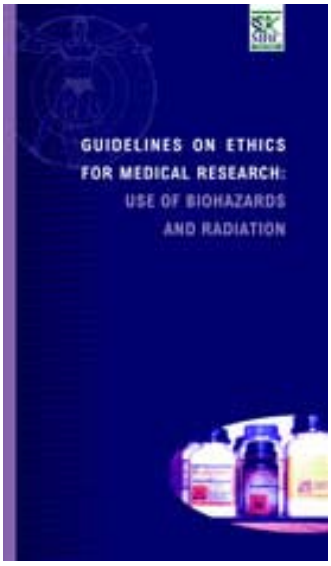
i. Determining genetic lesions in individuals has relevance in genetic counselling and in therapy, for example, and is covered in Book 2.
2. Where the health status of the patient indicates that the use of somatic gene therapy may be helpful, in the replacement of engineered bone marrow cells, for instance, provided the guidelines on ethics for working with humans are adhered to, the work may be regarded as ethical (see Book 2).
3. At this stage, manipulation of human germ-line cells is a complex issue and subject to the same guidelines as research in reproductive biology (see Book 2).

A number of other genetic engineering issues affect humans and animals less immediately or indirectly, but are nonetheless important. These include, but are not necessarily limited to:

i. the origins of the foreign gene or gene fragments;
2. the level of expression of the foreign gene;
3. whether the gene product is subject to post-translational modification and whether this process changes its nature;
4. the market sector targeted;
5. the potential benefit;
6. the possibility of legal or illegal export of the GMO and the potential for harm in a different environment;
7. whether the GMO will enter human or animal food chains;
8. potential toxicity of the new GMO;
9. potential allergenicity of the new GMO;
10. any effects that the GMO may have on the environment;

11. disposal of waste;
12. socio-economic impacts.

There are accepted protocols for evaluating many of these potential biohazards, ranging from assessing food allergenicity, **http://www.fao.org/WAICENT/FAOINFO/ECONOMIC/ESN/biotech.htm** and **http://www.who.int/fof** to the economics and politics of GMOs, **http://www.aphis.usda.gov/bbep/bp/OECD/usregs.htm** or biotechnology issues, **http://www.aphis.usda.gov/biotech/usda_biotech.html**, **http://www.aphis.usda.gov/bbep/** provides links to US web sites, **http://www.biodiv.org** provides links to EU documents. Scientific perspectives may be found at **http://biotech.nature.com**



Book 4: Use of radiation in research

7.1 Introduction

It is a general principle that the benefits of ionising radiation and radionuclides in medicine should outweigh the risk. Hence it is necessary to describe the risks and benefits of the proposed irradiations, noting whether the benefits are general, or specific to the people being studied. The description of the risks must include a quantitative estimate of the absorbed radiation dose and the means whereby exceeding any maximum dose will be prevented.

While irradiation of humans in medical research presents certain calculable risks, such irradiation, when properly controlled, carries a much smaller risk to health than many chemicals, pharmaceuticals and other agents in common use. Appreciable radiation exposure may sometimes be unavoidable in medical research, but the collective total exposure of people to irradiation for research purposes is normally considerably smaller than that incurred by the regular use of radiological procedures in diagnosis and therapy, and is frequently less than environmental exposure.

Non-ionising radiation is generally considered to be safe, but this assumption may not be valid for newer techniques. When these techniques are used in research projects, the issue of safety must be specifically addressed.

The International Commission on Radiological Protection (ICRP), established in 1928 by the International Congress of Radiology, has published comprehensive recommendations on the protection of man from ionising radiation, including recommendations on exposure in the context of medical research.11 In addition, the World Health Organisation published a report on the use of ionising radiation and radionuclides on human beings for medical research, training and non-medical purposes.12 The guidelines formulated by the South African Forum for Radiation Protection, as set out here, are based on the recommendations of these two bodies and are endorsed by the MRC.13 These bodies have also indicated methods for calculating absorbed radiation doses.

7.2 Types of research

7.2.1 Research involving radiopharmaceuticals

This type of research will involve the use of agents labelled with a radionuclide in order to evaluate their biokinetic behaviour. In some instances the radionuclide may be administered separately from the agent. Imaging of the subject may sometimes be necessary to assess the action of the therapeutic or other agent being used.

7.2.2 Research on new diagnostic applications

Most of this research is incidental to the irradiation of patients in the course of diagnosis and treatment, but it is sometimes necessary to evaluate normal subjects as well. The establishment of medical and biological reference values, based on an adequate selection of

known normal individuals, provides standards against which abnormalities can be judged. However, this should not include paediatric patients unless certain specific conditions, described below, are met.

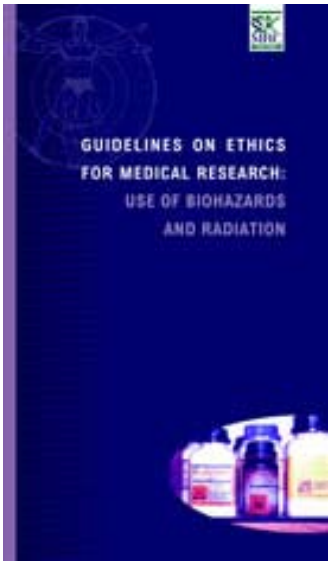
7.2.3 Treatment

The principles to be applied are essentially that (1) the therapeutic benefit should outweigh the risk and (2) the exposure should achieve a positive outcome while minimising side-effects (ALARA as low as reasonably achievable). In all cases, exposure should be based on Good Clinical Practice, whether it involves diagnosis, localisation, irradiation of the target, or minimising damage to the surrounds of the target and all other non-target regions.

7.2.4 Other research

This category covers studies in physiology, pathology and anthropology and includes studies on volunteers. It involves the use of compounds labelled with radioactivity to investigate, for instance, iron absorption, the fate of food additives and pesticides that are swallowed or inhaled, or injectables.

It includes research of epidemiological importance, and case-finding work in the field of industrial medicine and occupational health. It also involves patients being treated for various conditions, such as cancer, where radiation is a part of therapy.



Book 4: Guidelines

All MRC-supported medical research involving the use of ionising radiation and radioactive nuclides should be subject to the following general guidelines:

i. The irradiation of participants should be undertaken only by properly qualified and trained persons.
ii. Irradiation should have the approval of the institution's Research Ethics Committee.
iii. Approval should be based on the advice of an appropriate expert committee, and be subject to local and national regulations.
iv. Volunteer participants should fully exercise their free will and sign forms granting their informed consent.
v. The estimated irradiation risks should be explained to subjects.
vi. The magnitude of the risk to the volunteers should be authorised for each research programme.
vii. Calculations of absorbed dose must be made, if necessary with the assistance of experts in the field, and the results, with some indication of the methods used, should accompany any submission to an Ethics Committee.

Users of radioactive sources must familiarise themselves with the characteristics of the radiation sources they use, whether alpha, beta or gamma emitters, for instance, and the specific precautions necessary in the use of these sources. It is permissible for radiation workers to be exposed to higher doses of radiation than the general public, at present 1mSv per annum, but the ALARA principle (as low as reasonably achievable) in terms of dosage and exposure should be observed. Radiation workers must ensure that they or their institution are registered with the Department of Health for work with the source they wish to utilise. They should be properly trained and informed concerning use of that source. The maximum permissible dose for radiation workers is 20mSv per annum.

8.1 General

All appropriate experimental tests, whether in vitro or animal, should be carried out and assessed before commencing on research involving the exposure of humans. In all instances the doses received by the subjects should be kept to the minimum consistent with obtaining the desired information or therapeutic benefit. The guidelines on doses given hereafter are applicable to an entire project; that is, a complete scheme of research designed to achieve a particular objective.

8.2 Selection of volunteers

Because of the possibility of ionising radiation producing long-term deleterious genetic effects, human volunteers, wherever practicable, should be older than 40 and preferably over 50 years of age. Paediatric participants may be at greater risk than adults of suffering deleterious effects after receiving ionising radiation. Therefore, except in the most exceptional

circumstances, children should not be used as normal controls in research involving ionising radiation. However, where it is proposed that normal paediatric participants be irradiated, it is essential that such proposals be reviewed by several Ethical Committees, preferably located in different countries.

The number of volunteers participating in a project should be kept to the minimum necessary to obtain the required information with sufficiently small statistical uncertainty as accurately as possible, particularly when volunteers of reproductive age are used. Pregnant volunteers should be used only when problems specific to pregnancy are investigated. In these cases special consideration should be given to the embryo or fetus, with an estimate of its absorbed radiation dose and age at the time of administering the radioactive substances. The possibility of pregnancy occurring during the course of such research should always be borne in mind. Volunteers under the age of 18 years should be considered only in exceptional circumstances and when problems specific to their age are investigated.

8.3 Categories of research projects

Research projects should be classified according to the categories given hereafter. The distinction between categories is related to the total effective dose received by a research participant during 1 year. Examples should be provided of the types of benefits associated with research performed on persons in each of these categories.

8.3.1 Category I

The maximum permissible dose received by a research participant should not exceed 0,5 mSv which is the effective dose received as a result of natural background radiation, and is less than the effective dose received annually from this source of exposure.

8.3.2 Category II

The annual effective dose received by a subject may be greater than 0,5 mSv but less than 5 mSv. Thus the effective dose received will generally be of the order of that received as a result of natural background radiation.

8.3.3 Category III

The annual effective dose received by a subject may be greater than 5 mSv but less than 20 mSv. The effective dose received will generally be of the order of that permissible for occupational exposure.

8.3.4 Category IV

The annual effective dose received by a research participant may be greater than 20 mSv but less than 500 mSv. Research projects in this category should be permitted only in special circumstances. It would have to be convincingly demonstrated that the information required was important enough to justify the risks involved and that this information could not be obtained at lower dose levels.

8.4 Exposure of single organs

When organs or tissues are selectively irradiated, as is usually the case with research using radiopharmaceuticals and radiological examinations, higher doses to those organs and tissues may be permitted, with an overriding annual limit of 500 mSv for any single organ or tissue type. Calculation of the doses should be in accordance with factors given by the ICRP or other international regulatory and advisory bodies. Absorbed radiation doses to non-target regions must also be estimated.

8.5 Research proposals

A research proposal involving the exposure of human volunteers to ionising radiation should

include a detailed statement of the aims of the study; a full motivation of the need for the study; quantitative details of the radiation dosimetry; the source and nature of the radiation and the number and particulars of persons to be exposed. Dosimetric considerations should include absorbed radiation by non-target tissues, organs and systems, which almost inevitably occurs.

The research proposal should also include the nuclides to be used; their physical half- lives and the nature of the emitted radiation; as much information as is available on their likely distribution due to metabolism and translocation processes in significant organs and tissues; the biological half-lives of the radionuclides and radiopharmaceuticals as well as any daughter products. The statement should also specify the chemical form in which the radionuclide will be administered; details of the vehicle for administration and of any residual contamination, and information on the acute or possible latent toxicity of the chemical agent or vehicle. In respect of radiological examinations, this information should include the techniques and equipment to be used; the region of the body to be exposed and projections required; the number of exposures and/or screening time and the proposed technique factors, including field sizes. The proposal should also specify techniques, if any, for:

i. the reduction of the doses received by tissues in the region of the body under examination, to the minimum compatible with obtaining the necessary information;
2. the delivery to the treated region of the body of a therapeutic dose of a magnitude that is most likely to ensure the required response;
3. the limitation, as far as practicable, of the exposure of other parts of the body.

Dose estimates giving the maximum level of dose and its location should be provided, together with an assessment of the dosimetry by an independent expert such as a medical physicist. Furthermore, the provisions for radiation protection measures to the subject and all others who are associated with the radioactive material, whether actively or passively, and any other relevant aspects, should be fully described. Exposure should be limited to the maximum permissible dose as described by the International Committee of Radiation Protection. The means for preventing administration of a dose greater than the permissible maximum must be described.

Worker Safety

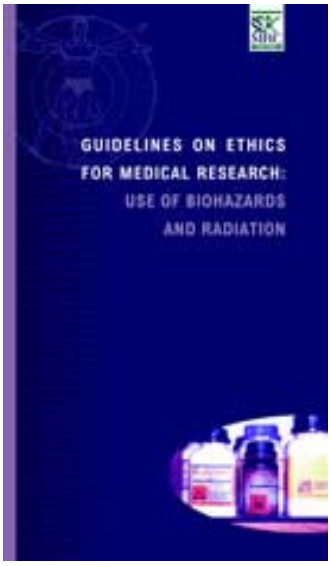
The institution must take steps to ensure application of the ALARA principle in terms of exposure to workers. The maximum permissible dosage for workers is higher than that permitted for the public and may also vary for different categories of personnel, such as radiologist or laboratory worker. In general, safety is related to spatial and temporal separation from radiation source, and may include physical and mechanical barriers.

8.6 Authorisation

In addition to the requirement that such irradiation should be given only with the consent of the authorities in charge of the institution where it is to take place, as advised by an appropriate expert body, the use of ionising radiation is subject to national regulations and prior authorisation from the Department of Health.

8.7 Radioactive waste disposal

Investigators have an ethical and legal obligation to ensure that legislated protocols for waste disposal are carried out as prescribed.14 Institutions also have a duty to ensure that all appropriate protective and waste-disposal measures are meticulously carried out.



Book 4: References

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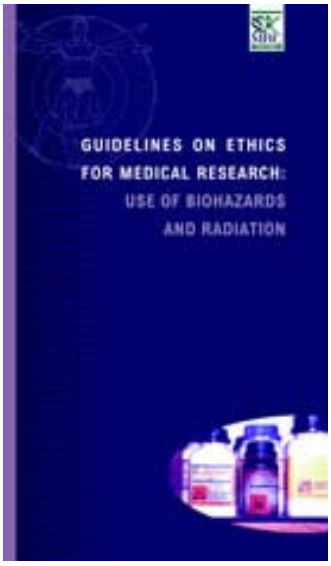

Book 4: Recommended websites for more information

1. International Atomic Energy Agency - **http://www.iaea.org**
2. International Commission for Radiological Protection -**http://www.icrp.org**
3. National Commission for Radiological Protection - **http://www.ncrp.org**
4. National Radiological Protection Board - **http://www.nrpb.co.uk**
5. Federal Drug Administration - **http://www.fda.gov**
6. World Health Organisation - **http://www.who.int/home-page**
7. Amersham - **http://www.amersham.co.uk**