

2. GUIDING PRINCIPLES

The purpose of this statement on ethical principles for health research in South Africa is to identify good, desirable and acceptable conduct, to protect the welfare and rights of research participants, and to reflect the basic ethical values of beneficence, justice and respect for persons. Both national and international accords and texts, outlined at Point 1.2 of this document, guide these principles and values.

Health researchers must conform to the following ethical principles and values, which must underscore all health research activities in South Africa.

2.1 Respects and Dignity

Respect for the dignity, safety and well-being of participants should be the primary concern in health research involving human participants. Culture, language, beliefs, perceptions, and customs must all be considered.

2.2 Relevance

Researchers in South Africa have ethical responsibility to ensure that their research is relevant both to the broad health and development needs of the country and to the individual needs of those who suffer from the diseases and concerns under study (Department of Health, 1999^a). The findings of the research must be translatable into mechanisms for improving the health status of South Africans.

2.3 Scientific Integrity

In addition to fulfilling a need and being of value, the research proposed must demonstrate sound methodology and a high probability of providing answers to the research questions posed. The research protocol must show knowledge of relevant literature, derived from a systematic review of that literature and, where appropriate, from laboratory and animal studies (National Health and Medical Research Council, 1998). Moreover, research methods and results must be open to peer review and scrutiny.

2.4 Investigator Competence

A suitably qualified investigator should conduct the study. The investigator's competence is assessed mainly by technical competence, which includes research competence, and is itself assessed in terms of education, knowledge, certification and experience. Compassion and empathy are among the characteristics required of a technically competent researcher. A proper clinical and research environment, encompassing good research mentoring, provides this. In all cases the local principal investigator must be a South African-based researcher; that is, one who is ordinarily permanently resident in South Africa.

2.5 Principal Investigator Responsibilities

The Principal Investigator (PI) must submit an application to the MCC and/or an appropriate and accredited local ethics committee. All clinical trials must be reviewed by the MCC and by a local ethics committee. Both of these reviewing institutions must approve the project before the study may commence. Principal Investigators bear full responsibility for the scientific and ethical aspects of their study, and are the means of communication with the ethics committee while obtaining approval. Once a study is in progress all reports of adverse events and management issues dealt with by the sponsoring company should be transmitted to the ethics committees, ideally through the Principal Investigator, who should be fully informed of these issues. To expedite the process, data could be

copied both to the Principal Investigator and to the ethics committee. However, it should be made clear that the Principal Investigator is responsible for the study. In addition, a system to ensure tracking of all research will be set up through the National Health Research Ethics Council and local ethics committees. This will involve each study being allocated a national study number and a position in the national database. It is envisaged that ethics committees will be allocated cohorts of notification numbers. When the data capturer has allocated a number to a particular project, this will be communicated to the National Health Research Ethics Council for inclusion in their database. A research project may not commence before receiving a national study number from the local ethics committee, which bears the responsibility of ensuring that the National Health Research Ethics Council receives a full list of numbers allocated.

The information in the national database should be available publicly, with the reservation that it be limited to information that would not jeopardise commercial interests. It is visualised that it would include:

- Title of research projects;
- Duration of the projects;
- PI name and affiliation.

A regular update of an anonymised research profile from database may be placed on the Department of Health's website with information such as:

- The number and proportion of studies by type (for example, trials or non-trials) proportions by study site
- Total sponsorship by type of study and study site

2.6 Informed Consent

Informed consent must be obtained from research participants before the research can begin. Both written and verbal informed consent must be obtained, unless there are good reasons to the contrary, such a situation of coma, emergency, or mental incapacity as indicated in 5.9 and 5.14 below. Prior approval of the ethics committee must be obtained in all situations in which it is justifiable to initiate research without the informed consent of the participant. Verbal consent, where the participant is illiterate, should be obtained in the presence of a literate witness who should verify in writing, duly signed, that informed verbal consent was obtained. Informed consent means that a participant has been informed about the risks and benefits of the research, understands such risks and benefits and is able to give consent to participation, without coercion, undue influence or inappropriate incentives.

In South Africa, researchers must be particularly aware of the vulnerability of prospective participants in terms of access to health services and education levels. Research details must be provided in a clear, simple and culturally appropriate manner. If a participant lacks capacity to exercise an informed choice to participate, an appropriate person to make the choice for them must be identified by the investigator. A participant is free at any time to withdraw consent to further involvement in the research, without having to face any unfair negative consequence or disadvantage. The following essential elements must be understood before a participant is capable of giving informed consent.

- That consent is being given to participate in research;
- The purpose of the research;
- The expected duration of the participant's involvement;
- A description of the procedures to which the participant will be subjected, including any experimental procedures that are innovative and have not been used in medical practice;

Prospective participants should be helped to arrive at an informed decision by, for instance, use of appropriate language, selection of a non-threatening environment for interaction and the availability of peer counseling. Participants may find information about the following points useful.

- The investigators' qualifications;

- Explanation of participants' responsibilities;
- Description of foreseeable risks or discomforts;
- Description of benefits to the participants or to others, both during and after the research;
- Disclosure of alternative procedures or courses of treatment;
- Description of the extent to which confidentiality will be maintained;
- Statement that sponsors of the study may be able to inspect research records;
- Statement that the research has been approved by an accredited research ethics committee;
- Contact details of research ethics committee representatives;
- Explanation as to whether compensation will be given for research-related injuries;
- Explanation as to the consequences of injury, including medical treatments;
- Explanation of whom to contact in the event of research-related injury.

Investigators must assure potential participants that participation is voluntary, and that refusal to participate, or a decision to discontinue participation, will not involve any form of penalty. The approximate number of participants should be disclosed. Details of treatment must be supplied and, where appropriate, the possibility of random assignment to various treatments or procedures must be made clear. The nature of experimental and control groups must be explained, as well as circumstances that might lead to the termination of participation.

Unforeseeable risks obviously cannot be foreseen, but participants must be told the nature and extent of risks – including financial risks – attendant on participation. Participants must be made aware of their right to be informed of relevant new findings, and of the consequences of their withdrawal from research. They should know, too, whether the investigator might terminate participation.

The above points may be regarded as essential elements of informed consent, and all should be incorporated in an Informed Consent Form or document.

Informed consent is a vital requirement in ethical conduct, and is valid only when it is obtained without deceit or misrepresentation. The informed consent requirements are not intended to pre-empt the laws of the country, which may require that additional information be provided to the participants. The moral duties of the medical practitioner or other investigator are in no way limited by these requirements.

2.7 Privacy and Confidentiality

In its simplest form privacy is concerned with access to personal records, while confidentiality refers to the use of personal information once it has been disclosed (Berglund, 1990). A participant's right to both privacy and confidentiality must be protected. The researcher must ensure that 'where personal information about research participants or a community is collected, stored, used or destroyed, this is done in ways that respect the privacy or confidentiality of the participants or the community and any agreements made with the participants or community' (National Health & Medical Research Council, 1998:5).

2.8 Inclusion and Exclusion Criteria

The selection, recruitment, exclusion and inclusion of research participants must be just and fair, based on sound scientific and ethical principles. No person may be inappropriately or unjustly excluded on the basis of race, age, sex, sexual orientation, disability, education, religious beliefs, pregnancy, marital status, ethnic or social origin, conscience, belief or language.

2.9 Risk and Benefits

A risk/benefit analysis of the study should precede the research itself. Risk/benefit analysis should take full notice of benefits and harms beyond the duration of the research, particularly in the case of chronic life-threatening conditions. Alternative ways of providing benefits to the participants might be available. The principal investigator has the ethical duty to exclude participants who might be placed at undue risk.

2.10 Publication of Results

Investigators have an obligation to disseminate research results, whether positive or negative, in a timely and competent manner. This is particularly important in clinical trials, where investigators are duty bound to ensure that findings are made public for all outcomes assessed. It is, however, important that the release of research findings be done in an ethical manner, to ensure that false expectations are not raised in a vulnerable population. Research results should not be prematurely released or published, or unreasonably delayed. It is advisable that the main results should be disseminated, using appropriate communication formats, to the participants and other interested members of the communities in which the study was conducted.

Results of a study, whether sponsored by government or industry, should be the intellectual property of the investigators, not the sponsor, and all results that have scientific merit should be published. Requests to withhold findings, to change or tone down the content of a report are not acceptable in good ethical practice. However, sponsors or stakeholders should be afforded the opportunity to comment on research findings prior to publication, without any entitlement to veto, change the conclusions, or unreasonably delay publication of results.

In collaborative research with pharmaceutical or other companies, the conditions of publication should be spelt out clearly in the protocol. Research ethics committees should be satisfied that there is no interference with the right to publish results.

2.11 Conflict of Interest

A researcher must disclose the sources and extent of funding to the research participants, the ethics committee and, where appropriate, to the regulatory authority. Commercial affiliations or financial interests at the time of proposing and reporting the research must also be disclosed.

2.12 Safety Monitoring

Safety monitoring of research activities is imperative, particularly in a clinical trial. This involves the prompt reporting of serious adverse events, including post-study events. It is the researcher's responsibility to ensure that adequate provisions are made to deal with any adverse event. The processes for this should be outlined in the research protocol.

2.13 Multi-Centre Studies

The number of multi-centre clinical trials and studies being undertaken in South Africa has increased dramatically in recent years. Prior to commencement of a study, approval should be obtained from the local research ethics committee. Designs should be appropriate to the local setting and particular modifications should be made to the local study when required, in the case of inclusion and exclusion criteria, for instance. It is unacceptable for developed-country participants to be offered better standards of care than are offered to South African participants in a similar study. In particular, when South Africa is chosen for a trial or study that has not been undertaken in the country of origin, an explanation should be sought as to why this is the case. In terms of study design, special attention should be paid to the sampling strategy. Other issues in international studies include financing of the

study, the appropriateness of incentive packages to research participants and remuneration packages for investigators.

Multinational Collaborative Research

The challenge to international research ethics is the development of universal rules for research at a time when health care is being delivered within very different health care systems (even within a single country) and in a multicultural world in which people live under radically different economic conditions. Variable trajectories of emancipation of individuals from community have also given rise to a wide spectrum of self-image, what it means to be ill and how health care systems should be structured. With recognition of the role of social conditions in shaping the world, and how privileged people view the world and themselves, comes the realisation that research cannot be considered in isolation. Medical research, health care, conditions of life around the world and how humans flourish may seem disparate, but all are interdependent. The global perspective adds complexity to the task of crafting universal guidelines for research ethics. It is necessary to ensure that:

- Benefits accrue to participants in the host country. Research with benefits limited to the sponsoring country is exploitative and unacceptable;
- The potential benefits of research considerably outweigh potential risks or harms to vulnerable individuals and communities;
- Research is non-exploitative and in the best interests of the research participants and their community;
- Groups already vulnerable are provided with improved access to research – in all countries;
- Research participants are encouraged to participate in planning and conducting studies;
- Research in developing countries is linked to capacity-building in health care, and to economic and educational empowerment to promote the delivery of health care and progress generally in the host country;
- Consideration is given to the risks and potential benefits to research participants, in proportion to the magnitude of benefit to sponsors;
- Honest efforts are made to translate research findings into components of accessible care in the community being researched;
- Conflicts of interest are avoided;
- Research protocols are modified to suit the situation in local communities;
- Publication of articles should be inclusive of investigators as authors from both host and sponsoring countries where appropriate contributions have been made.

2.14 Standard of care

In the past ‘standard of care’ has not been clearly defined. It has generally been assumed to refer to ‘drug treatments’. This is inadequate and the definition should be clarified and extended beyond consideration of drugs to consideration of other aspects of care that are either under the control of investigators or that could be influenced by them.¹

The provision of equal standards of medical care to all during research is a requirement for demonstrating equal respect for the dignity of research participants. An adequate definition of ‘standard of care’ should include:

- Equal respect for the human dignity of all participants irrespective of their location;
- Obtaining informed consent in the research participants’ home language, coupled with an understanding of their world-view or value system;

¹ Benatar S R, Singer P A. A new look at international research ethics. *Brit Med J* 2000; 321: 824-26.

- Provision of equal general care facilities, through access to the same modern technology and other external factors that may have contributed to the ‘best proven’ use of the drugs elsewhere, such as medications and care for other diseases, and access to advice and support to sustain compliance;
- The same follow-up facilities for research participants after completion of the study and the same access to ongoing care.

It is suggested that in determining the standard of care that should apply to research in developing countries it is not justifiable to be selective and choose only one aspect of a standard of care – such as drug treatment – without giving adequate reasons for such choice. In the absence of justification, the choice of only one of the elements of the standard of care may seem arbitrary. It may not be possible to meet all requirements in any developing country, but there are bound to be aspects of treatment or intervention that can be met immediately – those that are under the direct control of the investigator. It is suggested, then, that researchers from highly resourced countries bear some responsibility to promote better health care and research conditions by garnering additional support from partners in their own countries.²

2.15 Placebo-controlled studies

Research must be designed so that the foreseen benefits and risks to the research participants are equivalent in all aspects. The choice of intervention (placebo or some treatment) to administer to participants in the control arm of a study may require the balancing of many factors, but the welfare of participants must be paramount. The choice of control should be justified as part of the research protocol. Ethics review committees should verify that the control is appropriate, does not impose risks that are unreasonable in relation to the anticipated benefits, and that placebo controls are not employed without compelling justification. The research design should have the potential to yield scientifically valid results relevant to the population in which the research takes place.

Justifications for using a placebo in the control arm are that:

- No treatment or intervention is accepted as being effective for the condition;³
- Treatments or interventions are accepted as being effective for the condition, but the use of a placebo will not result in more than minimal adverse effects that are entirely reversible;
- Treatments or interventions are accepted as effective for the condition, but no scientifically justifiable control option, other than a placebo, meets the objective of the research, and the anticipated benefits of the research substantially outweigh the risks to participants.⁴

Exceptions to the general rule may thus be permissible in research where the foreseen benefits or risks may be greater in one or more arms, but sound scientific and ethical justification is provided in the research protocol. This imbalance should be clearly communicated to the ethics committee as well as in the informed consent procedure.

²Just as prison doctors, who have no direct influence over the conditions in which they treat prisoners, are expected to work towards better health care services for prisoners, so researchers from developed countries have an ethical obligation to improve the often deplorable conditions in countries in which they undertake research. Attention to such considerations will ensure that the overall conditions under which research is undertaken will continuously improve for the benefit of research participants and their community.

³ The UNAIDS Guidance Document (Ethical Considerations in HIV Preventive Vaccine Research, May 2000 (Guidance point 11, commentary) advises as follows:

"A vaccine with proven efficacy in preventing infection or disease from HIV does not currently exist. Therefore, the use of a placebo control arm is ethically acceptable in appropriately designed protocols. ... In an effort to address the concern of lack of benefit to those randomly placed in a placebo group arm, ... it is recommended that the provision to these persons of another vaccine, such as for hepatitis B or tetanus, be considered."

Other preventive interventions should also be offered so that participants may protect themselves.

⁴ This calls for judgement and legitimacy within specific contexts. Guidelines are less like instruction manuals and more like Constitutions that require interpretation.

A placebo-control group need not be untreated. In so-called ‘add-on studies’ the treatment to be tested and the placebo are each added to a standard treatment. Such studies are considered permissible where a standard treatment is known to decrease mortality or irreversible morbidity but a trial with standard treatment as the active control cannot be carried out or would be difficult to interpret (ICH Guideline: Choice of Control Group and Related Issues in Clinical Trials, 2000). In evaluating improved treatments for life-threatening diseases such as cancer, HIV/AIDS or heart failure, add-on trials are a particularly useful means of finding improvements in treatment or interventions that are not fully effective or that may cause intolerable side-effects. Such studies also have a place in treatment for epilepsy, rheumatism and osteoporosis, for example.

2.16 Ethical Review

All health research conducted in South Africa must be reviewed by a research ethics committee and should not commence until the ethics committee has granted approval. This provides an objective appraisal of the effect of the proposed research as it affects the potential participants and the general day-to-day functioning of the health system. Section 3 of this document outlines in more detail the process of ethical review in South Africa.

2.17 Distributive Justice

Research proposals should provide sufficient information to determine whether there is a reasonable likelihood that the population on whom research is to be carried out will benefit from the research and its results. Selection of participants from groups who are unlikely to be beneficiaries of subsequent applications of the research should also be justified. Research proposals should indicate whether long-term therapy would be provided to participants after the completion or termination of the study.