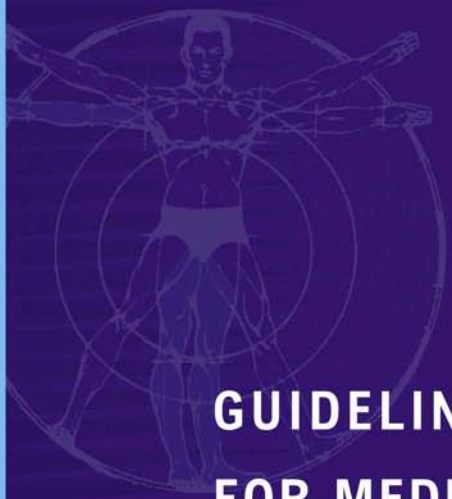

# GUIDELINES ON ETHICS FOR MEDICAL RESEARCH:

## HIV PREVENTIVE VACCINE RESEARCH

# Guidelines on Ethics for Medical Research

## Book 5: HIV Preventive Vaccine Research

This document is an adaptation of the UNAIDS (2000) publication *Ethical considerations in HIV preventive vaccine research*. Grateful and full acknowledgement of the source document is made.

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# 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:
    - 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?
    - 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
former MRC President

# 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/Modules/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, 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 HealthInfo website mentioned on page vi) 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 Preventive Vaccine Research.

# CONTENTS

# INTRODUCTION

In the third decade of the AIDS pandemic, there is still no effective HIV preventive vaccine. As the numbers of those infected by HIV and dying from AIDS increase dramatically, the need for such a vaccine becomes ever more urgent.

Several candidate HIV vaccines are at various stages of development. However, the successful development of effective HIV preventive vaccines is likely to require that many candidate vaccines be studied simultaneously in different populations around the world, requiring an international co-operative effort drawing on partners from health sectors, intergovernmental organisations, government, research institutions, industry, and affected populations. It also requires that these partners be able to address the difficult ethical concerns that arise during the development of HIV vaccines.

In the period 1997-99 the international organisation UNAIDS undertook to elucidate the ethical concerns around HIV preventive vaccines. Based on a series of consultative meetings,[1] UNAIDS generated a guidance document in 2000 which can be found at www.unaids.org. The UNAIDS (2000) document *Ethical considerations in HIV preventive vaccine research* forms the basis for the current text.

In 1999 the South African AIDS Vaccine Initiative (SAAVI) was established, with the aim of accelerating the development of safe and effective HIV vaccines for South Africa, and funded by such donors as the Departments of Health and Arts, Culture, Science and Technology, Eskom, International AIDS Vaccine Initiative, and National Institutes of Health.



In addition to funding candidate vaccine development, immunology, clinical trials, education and advocacy, SAAVI funded the HIV/AIDS Vaccines Ethics Group (HAVEG) at the University of KwaZulu-Natal to undertake research and training in ethical aspects of HIV vaccine research. In 2000 the Medical Research Council approached HAVEG to co-ordinate the development of ethical guidelines for HIV vaccine research in South Africa. HAVEG agreed to do so in consultation with national resource persons and ethics structures.

This document attempts to highlight some of the critical elements that must be considered in HIV vaccine development activities in South Africa and is conceptualised as a variant of the UNAIDS (2000) guidance document. Where necessary, adaptations have been made to take into account local context and considerations. In some cases, little change has been made to the original document.

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[1] For a full description of the process and participants, see *Final Report, UNAIDS-Sponsored Regional Workshops to discuss Ethical Issues in Preventive HIV Vaccine Trials*, available from UNAIDS. See also Guenter, Esparza, and Macklin: Ethical considerations in international HIV vaccine trials: Summary of a consultative process conducted by the Joint United Nations Programme on HIV/AIDS (UNAIDS). *Journal of Medical Ethics* 2000; 26,1: 37-43.

Where ethical considerations are adequately addressed by other existing texts, there is no attempt to replace these texts, which should be consulted extensively. This document makes reference to the Medical Research Council's Book 1 in this series, *Guidelines on Ethics in Medical Research: General Principles*. Efforts were made to harmonise this document with MRC Book 1, and the Department of Health's *Ethical Considerations for HIV/AIDS Clinical and Epidemiological Research*, and *Good Clinical Practice in the Conduct of Clinical Trials in South Africa*. Other codes relevant to HIV vaccine development include: the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, the International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS), the World Health Organization's Good Clinical Practice Guideline, and the ICH Good Clinical Practice Guideline.

It is hoped that this document will be of use to potential research participants, investigators, community members, government representatives, pharmaceutical companies, and ethical and scientific review committees. In the Preface, it was stated that South African ethical guidelines should emphasise the dignity and autonomy of the individual. There is also a need for South African guidelines to emphasise social justice among ethical principles, and this document attempts to do this.



The current document addresses a controversial area of research. Ethics symposia were held to discuss a number of the guidance points. A draft version was placed on the MRC website for public comment and over 200 comments were received. For certain guidance points, there were many different viewpoints and consensus was difficult to achieve. The current document aims to present aspirational guidelines for the conduct of HIV vaccine trials. Unlike Book 1 in the series, it does not present much legalese. All the points in this document are important and many are mutually dependent.

HIV vaccines are envisaged to be an important long-term preventive measure to combat the epidemic that has overwhelmed our country. Vaccine trials in search of suitable and effective vaccines should be designed and conducted according to high ethical standards. Standards for medical research, previously developed in South Africa exclusively by the South African Medical Research Council, are now being developed and set out by the National Department of Health through the Ministerial Committee on Health Research Ethics and the Medicines Control Council, with the support and collaboration of many individuals from several institutions. The National Department of Health acknowledges the extent of such collaborative work and endorses book 5: *Guidelines on Ethics for Medical Research: HIV Preventive Vaccine Research*, which has been developed by the Medical Research Council in close consultation with the Ministerial Committee on Health Research Ethics.

# CONTEXT

South Africa is experiencing an HIV/AIDS epidemic. The development of a safe and effective HIV vaccine has been identified as an urgent health priority.

At the outset, it must be emphasised that HIV vaccine development should be understood and approached within the context of a broader national South African programme of HIV prevention - a programme that, at the time of formulating these guidelines, still requires considerably more definition, coherence and co-ordination. Evidence suggests that a successful vaccine may not be fully developed and operational within the first decade of the 21st century. In the meantime, the epidemic spreads and is clearly attaining catastrophic proportions. Without denying the eventual value or importance of a vaccine, the best way to fight HIV/AIDS remains prevention. Everything possible ought to be done to establish an effective and realisable national programme to prevent this epidemic reaching unmanageable and socially catastrophic dimensions. The South African government must be supported by civil society and the private sector to take a firm and unequivocal lead in the establishment of such a programme.

The individuals and communities who will participate in HIV vaccine development activities require not only an effective HIV vaccine, but also to have their rights and welfare promoted while participating as active partners. Complex biological and social factors associated with HIV affect the balance of risks and benefits for individuals and communities who participate in HIV vaccine development activities, and include the following:



i) The burden of disease and death related to HIV is increasing at a rate unmatched by any other pathogen. In South Africa, HIV is the leading cause of death in adults.

ii) The context for access to effective treatment, antiretroviral medication, is transforming as drug prices are reduced, and regimens are simplified. However, antiretroviral medication is currently not readily available to the vast majority of people affected by HIV/AIDS in South Africa.

iii) There is an ethical imperative to urgently seek effective and accessible vaccines for South Africa, in conjunction with other prevention strategies. The impact of even a partially effective HIV vaccine may be of great public health benefit.

iv) Genetically distinct subtypes of HIV are predominant in different regions and countries, with subtype C being the most dominant subtype in South Africa. The relevance of subtypes to potential vaccine-induced protection is not clearly understood. Thus, it is not known whether a vaccine

targeted at one subtype will protect against infection from another subtype. It is likely that a vaccine directed at a particular subtype must be tested in a population in which that subtype is prevalent. Thus, developing a vaccine for populations with the highest incidence of HIV is likely to require that the vaccine be tested in those populations. This is the case even though these populations may be relatively vulnerable to exploitation and harm. Testing of vaccines based on other subtypes may be appropriate to investigate important questions, such as cross-clade reactivity.

v) South African HIV vaccine development is likely to involve multiple partners. While the term 'sponsor' usually refers to the individual or institution that owns the candidate vaccine or funds the vaccine programme (typically a single corporate entity, such as a pharmaceutical company), in modern vaccine development there are multiple sponsors, including corporations, national governments and international agencies. Some candidate vaccines may be manufactured in laboratories of sponsor countries (usually developed countries) and tested in South Africa (a middle-income country with severe economic disparities, where the majority of the population are of low economic status). The potential imbalance of this situation demands that differing interests and capacities of sponsors and host should be addressed. South African health and research communities should be encouraged and enabled to make decisions regarding participation in HIV vaccine development, based on identified health priorities, in a context of equal collaboration with sponsors.



vi) In South Africa those populations currently at highest risk of HIV infection are also vulnerable to potential harm and exploitation, due to a range of socio-historical reasons. Additional efforts are needed to overcome this vulnerability.

vii) HIV/AIDS is a condition that is both highly feared and stigmatised, largely because it is associated with blood, sex, and illegal activities such as commercial sex. As these issues are difficult to address openly, people affected by HIV/AIDS in South Africa experience stigma, discrimination, and even violence. Vulnerability to HIV infection is greater where people are marginalised due to their social or legal status. These factors increase the risk of social and psychological harm for people participating in HIV vaccine trials. Additional efforts must be made to minimise these risks, and to ensure that risks are justified by the benefits. Meaningful community participation and authentic informed consent are critical safeguards.

# 1. HIV vaccines development

**The severity of the HIV/AIDS pandemic in human, public health, social, and economic terms makes it imperative that sufficient capacity and incentives should be developed to foster the early and ethical development of effective vaccines. Sponsor countries and relevant international organisations should join with agencies in South Africa to promote HIV vaccine development.**

**1.1** Given the global nature of the pandemic, the devastation it is wreaking, the fact that vaccine(s) may be the best long-term solution by which to control the pandemic, and the potentially universal benefits of effective HIV vaccines, there is an ethical imperative for global support for the effort to develop HIV vaccines.

**1.2** This effort will require intense international collaboration and coordination over time, and will include countries with scientific expertise and resources, and countries and communities where candidate vaccines could be tested but whose infrastructure, resources and scientific and ethical capacities may be insufficient at present.

**1.3** Though HIV vaccines should benefit all those in need, it is imperative that they benefit the populations at greatest risk of infection. Thus, HIV vaccine development should ensure that the vaccines are appropriate for use among such populations, in which it will be necessary to conduct trials. When developed, the vaccines should be made available and affordable to such populations.



**1.4** HIV vaccine development activities take time, are complex, and require infrastructure, resources and international collaboration, therefore:

**1.4.1** Potential sponsor countries should immediately include HIV vaccine development in their regional and national AIDS prevention and control plans;

**1.4.2** South Africa as a host country should continue to develop HIV vaccine development in its national AIDS plans;

**1.4.3** South Africa should continue to participate in HIV vaccine development activities nationally and/or on a regional basis. Such activities should include identifying resources, establishing partnerships, conducting national information campaigns, strengthening its scientific and ethical sectors, and expanding its vaccine research to complement its other interventions;

**1.4.4** Potential sponsors and international agencies should make early and sustained commitments to allocate sufficient funds to make a vaccine a reality, including funds to strengthen ethical and scientific capacity where trials will have to be conducted and to purchase and distribute future vaccines; and

**1.4.5** Potential sponsors should establish partnerships with South Africa and undertake community consultations, strengthen necessary scientific and ethical components, and make plans for equitable distribution of the benefits of research.

## 2. Vaccine availability

**Any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials in which it was tested, and to other populations at high risk of HIV infection. Plans should be formed at the initial stages of HIV vaccine development to ensure such availability.**

**2.1** Given the severity of the pandemic, it is imperative that there should be sufficient incentives, both through financial rewards in the market place and through public subsidies, to foster development of effective vaccines while also ensuring that vaccines are produced and distributed so as to be available to the populations at greatest risk.

**2.2** There should be benefits to the host community, including access to the best proven prophylactic method identified by the study (see *Book 1, 11.4.4*).



**2.2.1** A safe and effective HIV vaccine should be made available as soon as possible to all participants in the trials in which it was tested, as well as other populations at high risk of HIV infection.

**2.2.1.1** In judging what is reasonable to expect in terms of current and future availability, international human rights standards should be used.

**2.2.2** As it will take a long time before a safe and effective vaccine is licensed and distributed, sponsors and investigators in collaboration with other stakeholders must consider how other benefits of HIV vaccine research are to be distributed in the participating community; that is, how research findings could be translated into components of health care (see *Book 1, 11.4.4*), capacity-building initiatives (see *Point 3*) and development of health care infrastructure (see *Point 16*).

**2.3** A process of discussion regarding making a safe and effective HIV vaccine reasonably available should begin among relevant parties before a trial commences, and should be carried on through the course of the research. The discussions should:

i. Include representatives of relevant stakeholders, such as the executive, health authorities, relevant scientific and ethical groups, participating communities, people living with HIV/AIDS, and NGOs representing affected communities;

ii. Include issues such as payments, royalties, subsidies, technology and intellectual property (see *Book 1, 11.4.2.ii*), and distribution costs, channels and modalities, including vaccination strategies, target populations, and dosage;
iii. Engage international organisations, sponsor governments, bilateral agencies, representatives from wider-affected communities, international and regional NGOs and the private sector;
iv. Consider financial assistance regarding making vaccines available; and
v. Build the capacity of government and communities to negotiate and implement distribution plans.

## 3. Capacity building

**Strategies should be implemented to build the capacity of South African institutions and communities to make meaningful decisions about HIV vaccine development, in full and collaborative partnership with sponsors and others, and to ensure the scientific and ethical conduct of HIV vaccine development activities.**

**3.1** South African communities have the right and the responsibility to take decisions regarding the nature of their participation in HIV vaccine research (see *Point 5.2*).



**3.2** Because of potential disparities in economic wealth, scientific experi-ence and technical capacity between investigators and communities, there is the potential for undue influence over and possible exploitation of South African communities.

**3.3** The many factors that may increase vulnerability to exploitation of communities in South Africa are outlined in *Book 1, 7.1.3.8.* Factors specific to groups from which potential HIV vaccine participants are likely to be drawn are outlined in *Point 7* and *Point 13.* Additional vulnerability factors include limited community experience with scientific research and limited political awareness of the importance and process of HIV vaccine research.

**3.3.1** Those who plan and conduct HIV vaccine research should identify relevant factors that increase potential harm to communities (see *Point 7*).

**3.3.2** Strategies must be undertaken by investigators and sponsors to offset such vulnerabilities and to promote a relationship of equality. These include:
i. Support to communities regarding information dissemination and capacity building programmes in the science and ethics of vaccine development (see *Point 6*), and consensus building on vaccine development;
ii. Early and sustained community involvement in the research process (see *Point 5*); and

iii. Transfer of knowledge and skills.

**3.4** The development of HIV vaccines for South Africa will require international collaborative research.

**3.4.1** There may be disparities between sponsors and South African institutions in terms of infrastructure, personnel and technical capacity for conducting the proposed research or for conducting scientific and ethical review.

**3.4.2** International research collaboration should transcend real or perceived disparities in a way that ensures equality in decision-making and action, and a relationship of collaboration among equals.

**3.4.3** All the principles governing international collaborative research identified in *Book 1, 11.1-4* apply to HIV vaccine development activities in South Africa.

**3.4.4** Strategies to promote a relationship of equality between South African and sponsor country institutions include:
i. Development of infrastructure and research capacity in South Africa (see *Book 1, 11.4.4.i*);
ii. Transfer of scientific knowledge and skills between sponsor countries and South Africa; and
iii. Support of the development of scientific and ethical review capacity (see *Point 6*).



## 4. Research protocols and study populations

**To conduct HIV vaccine research in an ethical manner the research protocol should be scientifically appropriate, and the desired outcome of the proposed research should potentially benefit the population from which research participants are drawn.**

**4.1** To be ethical, HIV vaccine trials should be based on scientifically valid research protocols. The scientific questions posed should be rigorously formulated in a research protocol that is capable of providing reliable responses.

**4.2** Valid scientific questions relevant to HIV vaccine development are those that seek to:
i. Gain scientific information on the safety, immunogenicity (ability to induce immune responses against HIV) and efficacy (degree of protection) of candidate vaccines;
ii. Assess safety in groups likely to be exposed in mass immunisation campaigns (e.g. HIV-infected persons) and in groups who would be targeted for immunisation (e.g. youth);
iii. Determine immunological correlates or surrogates in order to identify the

protective mechanisms and how they can be elicited;
iv. Compare different candidate vaccines; and
v. Test whether vaccines effective in one population are effective in other populations.

**4.3** The selection of the research population should be based on the fact that its characteristics are relevant to the scientific issues raised, and the results of the research should potentially benefit the selected population.

**4.4** The research protocol should:
i. Justify the selection of the research population from a scientific point of view (see also *Point 7*);
ii. Specify referral processes for those persons excluded from the trial, where relevant;
iii. Outline how the risks undertaken by the participants from that population are balanced by the potential benefits to that population (see *Points 9, 10, 14* and *16*);
iv. Describe the vulnerability factors of potential participants, where relevant (see *Point 7*);
v. Establish safeguards for the protection of research participants from potential harm arising from the research (see *Points 7* and *9*);
vi. Demonstrate how the candidate vaccine being tested is expected to benefit the population in which testing occurs; and
vii. Address particular needs of the proposed research population.



**4.5** Those who plan and conduct HIV vaccine research should have a good understanding of the social, political, health and cultural context of the specific community or population where the research will occur. This should be based on competent appropriate social science data (see *Book 1,11.4.3.iv*; and *Points 5 ,7, 9, 12.11, 13, 14.5* and *16*).

**4.6** The research endeavour should actively benefit the community being researched (see *Book 1, 11.4.3.iii*).

## 5. Community participation

**To ensure the ethical and scientific quality of the proposed research and its relevance and acceptability to the participating community, community representatives should be involved in an early and sustained manner in relevant aspects of HIV vaccine research, including the design, development, implementation, and distribution of results of HIV vaccine research.**

**5.1** In South Africa differences exist in status, knowledge and power between investigators and research participants, especially where participating individuals and communities are vulnerable because of socio-economic and other factors (see *Points 7* and *13*).

**5.2** The meaningful involvement of communities in research can serve to offset the vulnerability of communities and promote their rights and welfare. Furthermore, communities have the right and responsibility to take decisions regarding the nature of their participation in HIV vaccine research (see *Point 3.1*).

**5.3** Communities should be empowered to participate meaningfully in HIV vaccine development and research (see *Points 3* and *7*). Sponsors and investigators must commit the necessary time and resources required for such capacity development, and community participation.

**5.4** There should be community participation in all relevant aspects of HIV vaccine research. These include the design of HIV vaccine research, the development of HIV vaccine trial protocols, the implementation of the research and the distribution of research results.

**5.4.1** Investigators must clearly justify and explain those aspects of the research that are essential to a scientifically valid and ethically sound research design. Community participation should enhance the scientific quality or ethical soundness of the proposed research.

**5.4.2** Community participation should involve the review of ethical aspects of HIV vaccine research (see *Point 6*) and communities should be empowered in this regard (see *Point 3*).



**5.4.3** Community participation could include, but not be limited to, input into an appropriate informed consent process (*Points 12.2* and *12.5.2*), appropriate risk reduction interventions (*Points 14.2* and *14.5*), and decisions regarding treatment and care linked to the research (see *Point 16*).

**5.5** Community participation should:

i. Enable community members to become genuine and active partners in the research process;
ii. Be orientated towards mutual education and consensus-building regarding the research; and
iii. Be an ongoing and bi-directional communication process. Community involvement should not be seen as a single encounter, or as unidirectional.

**5.6** Community representatives should be chosen through a process of broad consultation.

**5.6.1** In this process, representative participation by community members and structures should be facilitated.

**5.6.2** Representation should encompass diverse sets of values and groups in the community, and be endorsed by primary socio-political structures. It should encourage the inclusion of relevant representatives from the following constituencies, for example:

i. The population eligible to serve as research participants;
ii. Relevant community-based and non-governmental organisations;
iii. Persons living with HIV/AIDS;
iv. Community leaders and public health officials;
v. Those who provide health care and other services to people living with and affected by HIV; and
vi. Other community members who would be among intended beneficiaries of a developed vaccine.

**5.7** Participants in the investigator-community partnership should develop a mutually respectful and evaluative ethos regarding their respective norms, conventions, values and expectations.

**5.7.1** Investigator and community representatives are encouraged to engage in a process of ethical reflection to develop a mutually agreed upon frame of reference that can be used to resolve disputes in a manner that protects the integrity of both partners.

**5.8** A continuing forum for communication and problem solving should be in place. Mechanisms for community participation include representation on existing structures, and/or the formation of new structures.

**5.8.1** There should be appropriate representation of the community on committees charged with the review and approval of the HIV vaccine research (see *Point 6*).



**5.8.2** The formation of new structures such as Community Advisory Boards (CABs) should be encouraged. A CAB consisting of community representatives could serve a number of critical functions. These include:
i. Information flow between investigators and participating communities;
ii. Education of the research team on community expectations, needs and values;
iii. Education of the community on aspects of the research;
iv. Evaluation of the impact of the research on the community; and
v. Voicing of community concerns.

**5.9** The expectations and hopes of the community should be identified early and the research team should explicitly address these expectations by clarifying which expectations can be met and to what extent.

**5.10** The potential benefits of community participation include:
i. Enhanced cultural appropriateness and quality of research questions;
ii. Forum to communicate and resolve concerns;
iii. Fairness and equity in a range of research decisions;
iv. Promotion of trust between investigators and community;
v. Effective dissemination of information to the community-at-large on the proposed research;
vi. Provision of information to investigators about health beliefs and norms of the community;

vii. Exchange of information about respective values and practices; and
viii. Facilitation of recruitment, retention and support of trial participants.

**5.11** In some instances it may be difficult to identify a 'community' or existing community structures and organisations (e.g. in informal settlements). However, investigators are encouraged to make every effort to identify and facilitate the development of structures and processes for community participation (see *Point 7.8.1*).

**5.12** The quality of community participation should be evaluated.

# 6. Scientific and ethical review

**HIV preventive vaccine trials should be carried out in South Africa only if the capacity exists to conduct appropriate, competent and independent scientific and ethical review.**

**6.1** Regulatory bodies and research ethics committees based in South Africa should review HIV vaccine protocols for such research to be conducted in South Africa.

**6.2** Where possible, committees that review HIV vaccine trial protocols should include appropriate representative membership from the community where the research will take place (see *Point 5.8.1*).



**6.3** These processes should ensure that the research is analysed from the viewpoints of individuals who are familiar with the conditions prevailing in the potential research population (see *Point 4.5*).

**6.4** Efforts should be made to build the capacity of community representatives to contribute to the development and review of HIV vaccine trial protocols (see *Points 3* and *5*).

**6.5** If capacity to conduct scientific and ethical review in South Africa is inadequate, the sponsor should be responsible for ensuring that adequate structures are developed for scientific and ethical review prior to the start of the research.

**6.5.1** Care should be taken to minimise the potential for conflicts of interest, while providing assistance in capacity building for scientific and ethical review.

**6.5.2** Capacity building may also be developed in collaboration with international agencies, or with South African organisations and parties.

**6.6** In the event of a dispute between review bodies, this dispute should be referred to appropriate national structures, such as the National Health Research Ethics Committee, for a process of resolution.

**6.7** Guidelines related to ethical review in *Book 1, Points 9* and *10* apply.

# 7. Vulnerable populations

**The social context of a proposed research population that creates conditions for possible exploitation or increased vulnerability among potential research participants should be assessed, where this is relevant. Steps must be taken to overcome these conditions, and to promote and protect the dignity, safety and welfare of participants. The vulnerability factors and steps that will be taken to offset these should be described in the research protocol.**

**7.1** Some communities, described as 'developing' or 'underdeveloped', may be considered as inappropriate participants for some phases of trials, due to a real or perceived increased level of vulnerability to exploitation or harm. These terms tend to refer primarily to economic considerations, whereas there are other relevant factors that affect risk.

**7.2.** Those who plan and conduct HIV vaccine research should explore and identify aspects of the social context that create conditions for exploitation or increased vulnerability to harm, for the selected pool of participants.

**7.3** Vulnerability factors affecting potential participants should be described in the research protocol, where relevant.

**7.4** Those who plan to conduct HIV vaccine research in vulnerable communities should justify this, and describe reasons why the research could not be conducted in less vulnerable communities (see *Book 1, 7.1.3.8*).



**7.5** Measures should be taken to overcome vulnerability factors, and these should be described in the research protocol.

**7.5.1** Strategies to offset vulnerability include capacity building for, and the early involvement of, participating communities (see *Point 5*), the development of advocacy processes and meaningful and ongoing informed consent procedures (see *Points 12* and *13*).

**7.6** In some potential research populations the conditions affecting vulnerability or exploitation may be severe. Where excluding such communities from the benefits associated with research seems inap-propriate, every effort should be made to afford adequate protection. If ensuring adequate safeguards is not possible, HIV preventive vaccine research should not be conducted in that community, and a less vulnerable community should be chosen (see *Book 1, 9.12.4.2.1*).

**7.7** Strategies to offset vulnerability should be rigorously evaluated. Trial counsellors, community structures and advocacy groups could play a useful role in this regard.

**7.8** General characteristics of vulnerable communities are described in *Book 1, 7.1.3.8*.

**7.8.1** Factors of particular reference to HIV vaccine research (see *Point 13*) include:

i. Social marginalisation of groups from which participants might be drawn, such as men who have sex with men and residents of informal settlements;
ii. Legal marginalisation of groups from which participants might be drawn, such as commercial sex workers and intravenous drug users;
iii. Junior or subordinate membership in hierarchical structures;
iv. Prevailing gender or class factors that limit ability to give free informed consent;
v. Limited availability and sustainability of health care and treatment options;
vi. Limited community structures, such as community-based organisations or forums; and
vii. Stigma or discrimination (social, institutional, governmental) on the basis of HIV status, or inadequate ability to protect HIV-related human rights, and to prevent HIV-related discrimination, including that arising from participation in an HIV vaccine trial.

**7.9** In South Africa many individuals at high risk of HIV infection (one eligibility criterion for participation in efficacy trials of HIV vaccines) may be simultaneously vulnerable to exploitation because of socio-historical factors, such as oppression and economic impoverishment.



## 8. Clinical trial phases

**As all clinical phases of vaccine development have their own particular scientific requirements and ethical challenges, the choice of study populations for each trial phase should be justified in advance in scientific and ethical terms in all cases, regardless of where the study population is found. Generally, early clinical phases of HIV vaccine research should be conducted in communities that are less vulnerable to harm or exploitation, usually within the sponsor country. However, South Africa may choose, for valid scientific and public health reasons, to conduct any phase within its own populations, if scientific infrastructure and ethical safeguards can be ensured.**

**8.1** Initial stages in a vaccine development programme entail research in laboratories and the use of animals.

**8.1.1** The transition from this pre-clinical phase to a phase I clinical trial, in which testing involves the administration of the candidate vaccine to human participants to assess safety and immunogenicity, is a time when risks may not yet be well defined.

**8.1.2** Specific infrastructures are often required in order to ensure the safety and care of research participants at these early stages.

**8.1.3** For these reasons, the first administration of a candidate HIV vaccine in humans should generally be conducted in less vulnerable research populations, usually in the country of the sponsor.

**8.2** South Africa, however, may choose to conduct phases I/II and/or III (large-scale trials to assess efficacy) among its own populations, including those that are relatively vulnerable to risk, after appropriate scientific, ethical and community consultation, for the following reasons:

**8.2.1** The experimental HIV vaccine is directed primarily towards a viral strain that does not exist in the sponsor country but does exist in South Africa. Conducting phase I/II trials may be the only way to determine whether safety and immunogenicity are acceptable in the South African population, prior to conduct-ing a phase III trial;

**8.2.2** The level of HIV risk in the population is so high, and the gravity of HIV/AIDS so severe that South Africa is willing to test an HIV vaccine concept that is not being tested in another country;

**8.2.3** Furthermore, if phase I and II trials are hosted in South Africa prior to phase III trials being initiated, this may result in important capacity building experiences (see *Point 3*) and opportunities to investigate important scientific questions.

**8.3** A South African vaccine development programme that entails conducting some, most or all of its trial components in South Africa, or in communities that are relatively vulnerable to harm or exploitation, is ethically justified if:



**8.3.1** The vaccine development programme is necessary for and responsive to the health needs and priorities of South Africa;

**8.3.2** The vaccine is anticipated to be effective against a strain of HIV that is an important public health problem in South Africa;

**8.3.3** Scientific and ethical review capability, and administrative and health infrastructure in South Africa are adequate to ensure the successful conduct of the proposed research;

**8.3.4** Research ethics committee members, community representatives, investigators and policy makers in South Africa have determined that participants will be adequately protected from harm or exploitation; and

**8.3.5** All other conditions for ethical justification, as set forth in this document, are satisfied.

**8.4** In cases where it is decided to carry out phase I or phase II trials first in South Africa, due consideration should be given to conducting such trials simultaneously in the country of the sponsor, where this is practical and ethical.

**8.5** Careful scientific and ethical consideration should be given to whether phase I and II trials that have been performed in a sponsor country should be repeated in the South African community in which phase III trials are to be conducted.

# 9. Potential harms

**The nature, magnitude, and probability of all potential harms resulting from participation in an HIV preventive vaccine trial should be specified in the research protocol, as fully as can be reasonably done. Active steps must be taken to reduce potential risks to a minimum. Such steps must be specified in the protocol, and should include provision of the highest level of care to participants who experience adverse reactions to the vaccine and compensation for research-related injury, and psychosocial and legal support as necessary.**

**9.1** Participation in HIV preventive vaccine research may involve physiological, psychological and social risks.

### 9.2 Potential physiological risks



The purpose of an HIV preventive vaccine is to induce an immunological response to counteract the HI virus if it enters the human body, or to prevent it from entering at all.

**9.2.1** Vaccines currently being considered for human trials in South Africa are not based on live attenuated approaches, and are not capable of causing HIV infection, i.e. they do not include replicating HIV.[2]

**9.2.2** Several candidate HIV vaccines have been tested in laboratories, and some have been tested in human participants. Not all of these candidate vaccines are the same, and not all candidate vaccines carry the same harmful potential. So far, however, significant adverse biological effects have not been observed.

**9.2.3** Nevertheless, some of the potential physiological risks of participating in vaccine research include:

i. A person who has received a candidate vaccine and is then exposed to HIV may, in theory, be more susceptible to infection, or to more rapid progression once infected, than if the vaccine had not been administered, although this potential harm has not been observed in trials thus far;[3]
ii. An HIV vaccine may require that several injections be given over months or years, resulting in pain, occasional skin reactions, and possibly other adverse biological events, such as fever and malaise; and

[2]Some of the most effective viral vaccines are based on live-attenuated viruses and some investigators have proposed a similar approach for HIV vaccines. Any decision regarding testing a live-attenuated HIV vaccine in humans would have to be carefully assessed in view of the significant safety concerns associated with such a vaccine approach.

[3]In HIV preventive vaccine research, the opposite effect is being sought.

iii. Injuries may be sustained due to research-related activities during the course of the trial.

**9.3** The potential for adverse reactions to the candidate vaccine, as well as possible injuries related to HIV vaccine research, should be described in the research protocol and fully explained in the informed consent process.

**9.4** There must be fair compensation for research-related injury, as laid out in the South African GCP Guidelines (see *Book 1, 11.4.4.iv* and *Book 1, Appendix IV*). The protocol must describe the nature of medical treatment to be provided for injuries, as well as compensation for harm due to research-related activities, and the process by which it is to be decided whether an injury will be compensated. This must also be fully explained in the informed consent process (see *Point 12.4*).

**9.5** HIV infection acquired during participation in an HIV preventive vaccine trial should not be considered an injury subject to compensation unless it is directly attributable to the vaccine itself, or to direct contamination through research-related activities.

**9.5.1** Every effort must be made to counsel volunteers against misplaced belief in vaccine efficacy, and to ensure that volunteers understand that the vaccine is experimental and may not afford protection (see *Points 9.7, 12.4* and *14*).



**9.5.2** Every effort must be made to provide participants with optimal risk reduction counselling and interventions to prevent HIV infection (see *Point 14*).

**9.5.3** Every effort must be made to ensure that counsellors involved in consent and risk reduction procedures understand the potentially harmful consequences of participants' mistaken belief that they may be protected from HIV infection (see *Point 14.6.6*).

### 9.6 Potential psychosocial risks

These include:

i Stress related to participation in a complicated, lengthy trial involving intensely intimate matters, and repeated HIV testing;
ii. Anxiety related to exposure to culturally different scientific and medical concepts;
iii. Stress that may result between partners in a relationship as a result of the participation of one partner in a trial;
iv. Stigma and discrimination that may result if volunteers' participation becomes publicly known, and they are perceived to be HIV-infected or at high risk of HIV infection;
v. A 'false-positive' HIV test that may result in the same negative social consequences that exist for those actually HIV-infected.[4] Some participants may develop a positive HIV test after receiving a candidate HIV

[4]Laboratory techniques can differentiate HIV-positivity due to vaccination from that due to actual HIV infection.

vaccine, even though they are not truly infected with HIV; and
vi. Stigma attached to participating communities that may be identified as high risk.

### 9.7 Risk minimisation measures

**9.7.1** Active steps must be taken to reduce potential risks to a minimum (see *Book 1, 9.12.4.7*).

**9.7.2** The protocol must describe potential risks, and steps that will be taken to reduce these risks to minimum.

**9.7.3** Participants must be informed of and should understand the risks and risk minimisation measures that will be taken, and these measures should be included in the informed consent form (see *Point 12*).

**9.7.4** Risk minimisation measures that should be taken include:

**9.7.4.1** Counselling participants against the belief that the experimental HIV vaccine will necessarily afford them protection, and ensuring that participants are provided with optimal risk reduction interventions (see *Point 14*).

**9.7.4.2** Rigorous and ongoing monitoring of potentially harmful consequences of trial participation (such as discord with family members or co-workers if a participant discloses participation, increase in high-risk behaviour over the course of a trial, or trial-related stigma or discrimination: see *Point 9.7.4.4*);



**9.7.4.3** Provision of supportive counselling for the duration of the trial, and appropriate referral after the trial is completed;

**9.7.4.4** Provision of measures to anticipate and offset trial-related stigma and discrimination, including:
i. Provision of documentation to participants to indicate that they are participating in research, that their false-positivity is research-related, or that facilitates access to trial personnel for assistance. Such documentation could take the form of an identification card. Any such documentation must take into account confidentiality or stigma concerns related to the terms 'HIV' or trial phase;
ii. Provision of differential testing, for as long as false-positivity persists. Investigators must ensure that participants will not have to bear the financial burden of differential testing for HIV infection; and
iii. Provision of legal support for trial-related negative consequences, such as discrimination attendant on false-positivity.

**9.7.4.5** Ensuring, once the trial is complete, that participants will have access to support services for trial-related negative consequences, and that participants are informed of where such services may be obtained;

**9.7.4.6** Ensuring that the research takes place in communities where confidentiality can be maintained; and

**9.7.4.7** Ensuring access to an ombudsperson who can intervene with outside parties, if necessary and requested, on behalf of participants.

**9.8** In non-therapeutic research, such as trials of HIV preventive vaccines, healthy volunteers should be subject to no more than minimal risk as a result of participation, even if the particular research will be of great benefit to humanity (*Book 1, 9.12.4.4.2*). Minimal risk is defined as a small chance of a trivial reaction or a very remote chance of serious injury or death (*Book 1, 9.12.4.3.2*). The risk should be justifiable in relation to the value of the information being sought.

**9.9** Research ethics committees must consider whether risks inherent in the proposed research are at an acceptable level, whether they have been reduced to the minimum necessary to achieve the research objective, and are outweighed by the probable benefits (see *Book 1, 9.12.4.7-9* and *Point 6*).

**9.10** Prior and ongoing consultation with community representatives should take place to assess potential risks that should be brought to the attention of investigators (see *Point 5*).

## 10. Benefits



**Efforts must be made to maximise the potential benefits of HIV preventive vaccine research. The research protocol should outline the benefits that participants in HIV preventive vaccine trials should experience as a result of their participation.**

**10.1** Some of the activities related to the conduct of HIV vaccine trials should benefit participants.

**10.1.1** At a minimum, participants should:

i. Have regular and supportive contact with health-care workers and counsellors throughout the course of the trial (see *Point 12*);
ii. Receive comprehensive information regarding HIV trans-mission and how it can be prevented, and access to appropriate HIV prevention methods, including barrier methods (see *Point 14*);
iii. Have access to treatment and care for HIV/AIDS if they become HIV-infected while enrolled in the trial (see *Point 16*); and
iv. Receive compensation for travel, time and inconvenience relating to trial participation.

**10.1.2** If the vaccine is effective, recipients may develop protective immunity to HIV infection or disease.

**10.2** Expected benefits should be described in the research protocol

presented to research ethics committees, and in the informed consent process.

**10.3** Care should be taken that benefits, such as superior attention and improved treatment and care (see *Point 16*), are not presented in a way that unduly influences freedom of choice regarding participation (see *Book 1, 9.13.2.1/2* and *Point 12.8.3*).

**10.3.1** Community representatives should be consulted to assist investigators to distinguish between benefits and undue inducements for participants and participating communities, taking into account local conditions (see *Point 12.8.3*)

**10.4** Where participants incur expenses as a consequence of their participation, it is proper that they should be reimbursed for that expenditure (see *Book 1, 9.13.2.4*). Some payment for inconvenience or discomfort may also be considered reasonable (see *Book 1, 9.13.1*).

**10.4.1** All payments to participants should be declared to and approved by local research ethics committees.

**10.5** Investigators should communicate the results of the research to participants and participating communities, and the mechanism by which this will be done should be specified in the protocol.



**10.6** Some benefit should accrue to the participating community as a result of HIV vaccine development activities, such as capacity building initiatives (see *Book 1, 11.4.4; Points 2* and *3*).

## 11. Control group

**As long as there is no known effective HIV preventive vaccine, a placebo control arm should be considered ethically acceptable in an HIV preventive vaccine trial.**

**11.1** 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.

**11.2** Participants in the control arm of future HIV preventive vaccine trials should receive an HIV vaccine known to be safe and effective when such is available, unless there are compelling scientific reasons which justify the use of a placebo.

**11.2.1** Compelling scientific reasons to use a placebo rather than a known effective HIV vaccine in the research population include:

i. Evidence that the HIV vaccine is highly unlikely to be effective against the

virus that is prevalent in the research population; and

ii. Convincing reasons to believe that the biological conditions that prevailed during the initial trial demonstrating efficacy were so different from the conditions in the proposed research population, that the results of the initial trial cannot be directly applied to the research population under consideration.

**11.3** All participants should receive the benefit of active promotion of HIV preventive interventions (see *Points 10* and *14*).

**11.3** Based on scientific requirements, the balance of risks and benefits to active versus control arms, and the wishes of participants, due consideration could be given to the use in the control arm of a vaccine to prevent a relevant condition other than HIV .

## 12. Informed consent

**Independent and informed consent for participation, based on complete, accurate, and appropriately conveyed and understood information as well as its consequences, should be obtained from each individual who is legally competent to give consent. Consent should be obtained for screening for eligibility for participation in an HIV preventive vaccine trial, and before a participant is actually enrolled in a trial. Throughout the trial efforts must be made to ensure that participants continue to understand the consequences of participation and that they participate freely as the trial progresses. Informed consent, with pre- and post-test counselling, should also be obtained for testing HIV status before, during, and after the research.**



**12.1** The purpose of informed consent is to foster considered decision-making by potential trial participants, including refusal to participate, based on respect for each person's autonomy and right to self-determination.

**12.1.1** Investigators should facilitate decision-making for potential participants, who should be empowered to make decisions that are consistent with their values and preferences (see *Book 1, 5.3.2.3*).

**12.1.2** Informed consent is a vital means of ensuring that trials are ethical, and should not be viewed primarily as legal indemnification for investigators.

**12.2** Before the start of the research it is recommended that a process of consultation between community representatives, investigators, research ethics committees, regulatory bodies, and sponsor(s) be undertaken to design an effective informed consent strategy. Where appropriate, this consultative process should be supported by capacity building.

**12.2.1** Issues affecting decision-making, such as illiteracy, language, cultural norms, and diminished personal autonomy should be addressed in this consultative process.

**12.2.2** With vulnerable communities and participants, special efforts must be made to achieve adequate understanding of relevant technical concepts or procedures, such as 'placebo' or 'double blind', and the personal implications of trial participation.

**12.2.3** Pre-trial consultations should provide for assistance to participants in the event of physical or psychological harm to themselves or their families as a result of trial participation (see *Point 9*).

**12.3** Trial staff and counsellors should be sufficiently trained to ensure adequate informed consent (see *Book 1, 9.6.2*).

**12.3.1** Trial staff and counsellors should:

i. Establish an optimal emotional context for the exploration of information;
ii. Be sensitive to the interpersonal interaction between themselves and participants;
iii. Facilitate participants' understanding of technical concepts and their consequences, and the personal, psychosocial implications of trial participation;
iv. Facilitate considered decision-making by trial participants, including withdrawal or refusal to participate;
v. Assist with personal concerns arising from trial participation;
vi. Evaluate the impact of the trial on participants; and
vii. Provide feedback to investigators to adapt and improve consent procedures.



**12.4** The disclosure duties of investigators are meticulously detailed in *Book 1, 5.3.2.3*.

**12.4.1** In addition, each prospective participant must be counselled, using appropriate language and techniques, to understand the following specific information:

i. That they will receive counselling and access to the means of risk reduction but that in spite of these efforts, some may become infected with HIV;
ii. That it is not known whether the experimental vaccine will prevent HIV infection or disease, and that some of the participants will receive a placebo instead of the candidate HIV vaccine (when such is the case). Therefore, they cannot assume that trial participation will afford them protection from HIV infection (see *Points 9* and *14*);
iii. That participants in phase II and III trials have been selected because they are at relatively high risk of HIV infection;
iv. The potential specific risks for physical, psychological and social harm; how these will be minimised, and the types of treatment, compensation and services that will be available should harm occur (see *Point 9*);

v. The nature and duration of care and treatment that is available if they become infected with HIV during the course of the trial, and any benefits to them personally or to their community that might be expected from participating in the trial (see *Points 3, 10* and *16*);
vi. The confidential nature of their participation, and the limits of confidentiality where these apply (see *Book 1, 6.6* and *7.2.3*);
vii. That they are free to participate, or to withdraw at any time without adverse consequences; and
viii. The expected time when results will be made available to them.

**12.5** Information transmission should be viewed as a bilateral process between investigators/counsellors and prospective participants. Investigators and counsellors should make every effort to apprise themselves of the life circumstances, expectations and motivations of prospective participants.

**12.5.1** Investigators and counsellors should attempt to understand the implicit and explicit expectations of participants, in order to pre-empt any misunderstanding or sense of exploitation (see *Point 5.9*).

**12.5.2** Investigators should consult with community representatives to assess cultural issues relevant to the transmission of information, and to determine the best procedures for transmitting information (see *Point 5*).

**12.6** Trial participants must have an adequate understanding of the aims, procedures, duration, potential risks, expected benefits, and personal implications of trial participation. They should also understand their rights as participants.



**12.6.1** True understanding will require that trial information is understood in terms of the participant's personal, or religious and cultural values.

**12.6.2** Participants' short-term recall of technical information about trials is not an adequate indication of understanding.

**12.6.3** A range of procedures should be used to assess both understanding of technical terms (e.g. placebo) and understanding of the personal implications of participation (e.g. possible stigma or discrimination). Assessment procedures might include check-lists of understanding of technical information, as well as responses to narratives or vignettes related to participation.

**12.6.4** Procedures to assess understanding could be developed in consultation with community repre-sentatives.

**12.6.5** Trial staff should be aware of the phenomenon of 'social desirability'; that is, the tendency for participants to act in order to win the favour of investiga-tors. Social desirability may affect reported or expressed understanding. Trial staff should be sensitive to this phenomenon and to the unexpressed reservations of participants. Neutral advisors (see *Book*

*1, 5.4*) and appropriately trained counsellors (see *Point 12.3*) may play a role in promoting understanding among research participants.

**12.7** Legal requirements for capacity to consent must be met. Persons above the age of 18 years, who are of sound mind, are generally considered capable of giving independent informed consent for participation in research. If other requirements are met, when persons below the age of 18 years are to be involved in research, proxy consent must be secured from a parent or legal guardian. In certain circumstances persons below the age of 18 years are considered able to give their own consent. This is discussed in more detail under *Point 18*.

**12.8** Respect for autonomy and self-determination are the foundation of informed consent. Consent must be voluntary and freedom of choice must be safeguarded (see *Book 1, 5.3.2.4*).

**12.8.1** Investigators must make every effort to assess conditions that may threaten the autonomy of participants (see *Book 1, 5.3.2.4.1*; *Points 7* and *13*).

**12.8.1.1** Participants may attempt to win the favour, and avoid the disapproval, of investigators because of real or perceived differences in power between investigators and participants, and the real or perceived benefits of trial participation. This 'social desirability' may lead participants to express socially desirable views rather than views based on personal needs and values, for example, about the acceptability of trial procedures.



**12.8.2** Investigators must introduce measures to reduce potential threats to autonomy and free consent. These are discussed in *Point 13*. Trial counsellors (see *Point 12.3.1*) or community representational structures (see *Point 5*) might also play a valuable role in voicing the needs and concerns of trial participants.

**12.8.3** Undue inducements, offers that persuade participants to volunteer against their better judgement or to assume risks that they would not otherwise have assumed, should be avoided (see *Book 1, 9.13*). Investigators should consult community representatives for assistance in making appropriate distinctions, with regard to local conditions, between legitimate benefits and undue inducements.

**12.9** After careful consideration of the implications of trial participation, prospective participants will decide whether to participate or not. If they choose to participate, a record of their explicit consent should be obtained, through the signing of the informed consent form.

**12.9.1** While the formal record of consent is important, it can never substitute for the process of informed consent. Where participants are illiterate, alternative procedures may be negotiated, such as providing a thumbprint in the presence of approved witnesses.

**12.9.3** Informed consent forms should contain sufficient information about the trial procedures, and their consequences for participants, to ensure a clear understanding of relevant considerations, without being complicated by excessive information.

**12.9.4** In exceptional cases, prospective participants may refuse to have a formal record of participation. *Book 1, 5.2* outlines that written informed consent may be waived only in certain compelling circumstances, and the necessary protections and regulatory requirements must be met.

**12.9.5** An appropriate interval should be allowed between counselling and obtaining explicit formal consent.

**12.10** HIV vaccine trials require informed consent at a number of stages. The first stage consists of screening candidates for eligibility to participate, which will involve, among other things, an assessment of the individual's risk-taking behaviour and a test for HIV status.

**12.10.1** Informed consent should be obtained during screening, after the candidates have received all material information regarding the screening procedures and their consequences, as well as an outline of the vaccine trial in which they will be invited to enrol, if found eligible.

**12.10.1.1** Informed consent should also be obtained for the test for HIV status. This should be accompanied by appropriate pre-test and post-test counselling, and referral to appropriate clinical and social support services, if found positive (see *South African GCP Guidelines, 9.3* and *9.4.1*).



**12.10.1.2** Procedures should be set in place to protect people from possible breaches of confidentiality and negative consequences arising from exclusion from trials on the basis of HIV status.

**12.10.2** The second stage at which informed consent is required occurs when a person is judged eligible for enrolment.

**12.10.2.1** The nature and duration of the trial, potential risks and expected benefits, should be explored and discussed through appropriate methods (see *Points 12.4* and *12.6*).

**12.10.2.2** Participants should understand that they are not obliged to participate and are entitled to with-draw from the trial at any time without suffering any loss of benefits to which they would other-wise have been entitled (see *Point 12.4.1*).

**12.10.3** After enrolment, participants should give ongoing explicit assurance that their continued participation is based on free consent and understanding.

**12.10.4** Informed consent, with pre- and post-test counselling, should be obtained for any repeated tests for HIV status.

**12.11** A distinction should be drawn between the substantive ethical standard of informed consent and the procedures for the implementation of informed consent. The standard of informed consent should always apply, but the procedures for the most effective implementation of informed consent may vary. Investigators should be sensitive to local, culturally based norms that may affect procedures for obtaining informed consent, but these should not compromise fundamental substantive ethical standards.

**12.11.1** In many South African communities it is customary to obtain the permission of community leaders or other designated authorities for investigators to enter the community to invite individual members to participate in research. Investigators should respect such norms and attempt to incorporate them in a spirit of collaboration (see *Book 1, 11.4.1*). Permission to enter communities should be distinguished from individual informed consent.

**12.11.2** Local norms may require that prospective participants, especially women, obtain the approval of other persons (such as marital partners, heads of households) to participate in a trial (see *Point 13*). Practices based on such norms must never be used as a substitute for individual informed consent, which must always be obtained from the prospective participant.

**12.11.3** Investigators should recognise that personhood in the African context is essentially defined by relationship, and that relationships will be important for many trial participants in South Africa. Explicit procedures should be in place to accommodate partners and family in the process of decision-making, if the participant so chooses. If the participant agrees, trial counsellors and staff should be available to the participant's partner or family, to discuss trial-related concerns and questions.



**12.11.4** Investigators should also protect the right of individuals to choose not to involve partners or families in the process of decision-making. Care should be taken to consider and offset any potentially harmful social consequences of such a choice.

**12.11.5** At times there may be conflict between respect for individual autonomy and regard for the participant's relationships with other individuals and the community. Every attempt should be made to protect both values; however, respect for individ-ual consent should always receive priority.

# 13. Informed consent: Special measures

**Special measures should be taken to protect persons who are, or who may be, limited in their ability to provide informed consent.**

**13.1** There are several categories of persons who are legally competent to consent to participate in research, and who have sufficient cognitive capacity to consent, but who may be limited in their freedom to make independent choices.

**13.2** Those who plan, review, and conduct HIV vaccine trials should be alert to the problems presented by the involvement of such vulnerable persons. Appropriate steps must be taken to identify and offset their vulnerability. If it is not possible to address the vulnerability of such persons, they should be excluded from participation in trials. The involvement of vulnerable participants should be subject to the condi-tions outlined in *Point 7*.

**13.3** Categories of vulnerable persons are described in *Book 1, 5.3* and *7.1.3*. For HIV preventive vaccine trials such persons may also include:

i. Persons who engage in illegal activities, such as commercial sex workers, or intravenous drug users. Such persons are vulnerable to undue influence and threats presented by possible breaches of confidentiality and action by legal forces. Persons engaging in socially stigmatised activities may be vulnerable to similar pressures; for example, men who have sex with men (see *Point 7*);
ii. Persons who are junior or subordinate members of hierarchical structures, including members of the armed forces, students, employees and prisoners. Such persons are in dependent relationships (see *Book 1, 7.1.3.7*) and may be vulnerable to undue influence or coercion in that they may fear retaliation if they refuse co-operation with authorities (see *Point 7*);
iii. Women living in cultures where their autonomy as individuals is not sufficiently recognised. They might be vulnerable to coercion from male partners, family, community members or traditional leaders (see *Points 7* and *12.11*); and
iv. Persons from resource-poor communities or those dependent on welfare programmes. Such persons may be vulnerable to undue influence through offers of what others may consider modest material inducements (see *Point 7*).

**13.4** Those who plan and conduct HIV vaccine trials should ensure meaningful, independent, ongoing informed consent of vulnerable persons, should respect their rights, foster their well-being, and protect them from harm (see *Points 9* and *12*). Extra efforts that should be taken to ensure this include:

i. Counselling to facilitate decision-making and to explore the impact of participation on such persons;
ii. Evaluation of consent processes by an independent advocate,

ombudsperson or group, or trial monitor;
iii. Ongoing evaluation of potentially negative consequences related to trial participation; and
iv. Access to supportive counselling and psychological and legal support services for trial-related harmful consequences, where necessary.

## 14. HIV risk-reduction interventions

**The most appropriate risk-reduction counselling and access to preventive methods should be provided to all trial participants, with new methods being added as they are discovered and validated.**

**14.1** Reducing the risk of HIV infection among participants is an essential ethical component of HIV preventive vaccine trials (see *Points 9* and *10*).

**14.1.1** This is especially critical given that phase III efficacy trials rest on some exposure to HIV infection. In order to manage the perceived conflict of interest between risk reduction and scientific goals of the research, and to promote the welfare of participating individuals, investigators are morally compelled to provide optimal risk-reduction measures to participants. This is clearly captured in *Book 1, 3.1.3 x*, which states that research objectives are subordinate to the principle that human beings should be treated with respect.



**14.2** It is recommended that before the start of a trial, a process of consultation between community representatives, investigators, host government and sponsors be used to design an effective risk-reduction strategy and its parameters. The local research ethics committee should approve the risk-reduction strategy.

**14.3** The most suitable parties to be risk-reduction counsellors should be considered.

**14.3.1** This should take into account factors such as real or perceived conflicts of interest for trial counsellors, local capacity building and sustainability, and protection of participant confidentiality regarding participation.

**14.3.1.1** In order to provide a contribution of lasting benefit to the participating community, consideration could be given to developing the capacity of community members to provide counselling. To prevent any real or perceived conflict of interest, consideration could be given to utilising counsellors from an independent organisation.

**14.3.1.2** All risk-reduction counsellors should be provided with appropriate training, supervision and sup-port, including ethical responsibilities, lines of accountability and, if necessary, anticipated personal and professional conflicts.

14.4 All trial participants should receive comprehensive risk-reduction counselling and methods to decrease risk of HIV infection. As new methods of prevention are discovered and validated, these must be added to the preventive methods offered to trial participants. Preventive methods should include, but not necessarily be limited to:

i. Basic principles of risk-free and safer sexual practices;
ii. Education concerning general health and identification and prevention of sexually transmitted infections (STIs);
iii. Appropriate access to barrier methods, such as condoms, during every counselling session and on every other contact with the trial site, and participants should be informed where barrier methods are locally available between visits;
iv. Treatment of STIs. Simultaneously, participants should be informed how to obtain treatment for their partners; and
v. Counselling around the potential benefits and risks of post-exposure prophylaxis with antiretroviral medication, and how it can be accessed.

**14.5** HIV prevention counselling can be a most effective mechanism through which to facilitate personal behaviour change.
Counselling should be:

i. Conducted in accordance with recognised national counselling guidelines;
ii. Appropriate to participants' culture, language, gender and age; and
iii. Based on reliable information about the prevailing social and behavioural characteristics of the research population.



**14.6** Theoretical behaviour-change principles should be used to assist participants to identify and modify personal behaviour that places them at risk of acquiring or transmitting HIV infection.

**14.6.1** While the standard approach to voluntary counselling and testing (VCT) in South Africa is the single pre-test and post-test counselling session, trial counsellors are encouraged to offer enhanced counselling encounters, which are likely to be more effective in encouraging safer sex behaviours.

**14.6.2** While a directive, educative, health-advising orientation predominates in current HIV/AIDS counselling, trial counsellors are encouraged to adopt an interactive, facilitative approach to assist participants to make a range of decisions in their own best interests (see *Point 12*).

**14.6.3** After consideration for the autonomous choice of participants, and protection of their welfare and privacy, counsellors might adopt flexible alternatives to individual counselling, such as couples' counselling, based on the influence of interpersonal relationships on individual behaviour.

**14.6.4** Counselling should aim to assist at-risk participants to avoid infection, and assist participants who become infected to modify their behaviour so as to minimise the risk of HIV transmission. Counselling should

also assist infected participants to maximise their quality of life and their psychosocial well-being.

**14.6.5** Trial participants should be counselled about the dangers of presuming that an experimental vaccine can prevent HIV infection, and about the potential for a false sense of security and increased risk behaviour (see *Points 9.5* and *12.4*) .

**14.6.6** Every effort must be made to ensure that counsellors involved in risk-reduction procedures understand the potentially harmful consequences of participants falsely believing that they are protected from HIV infection (see *Point 9.5.3*).

## 15. Monitoring informed consent and HIV risk-reduction interventions

**A plan for monitoring the initial and continuing informed consent process, and for evaluating the quality of risk-reduction interventions, should be agreed upon before the trial commences and be implemented throughout the trial.**



**15.1** The method and process for monitoring informed consent and risk-reduction interventions should be designed and agreed upon by the partnership of community, host, government, investigator and sponsors.

**15.2** Plans to monitor consent, and risk-reduction interventions, should be submitted for approval to local research ethics committees.

**15.3** The value of informed consent depends primarily on the ongoing quality of the process by which it is conducted, and not on the structure and content of the informed consent document.

**15.3.1** Explicit consideration should be given to mechanisms and personnel for the evaluation of the quality of the informed consent process.

**15.3.2** Steps that might be taken include: training counsellors to evaluate the experiences of participants and to provide feedback in order to revise aspects of the informed consent process.

**15.3.3** Evaluation and revision should aim to optimise sound decision-making of current and future participants.

**15.3.4** All recommended revisions should be within the parameters approved by local research ethics committees.

**15.4** Risk-reduction interventions should be evaluated to ensure that quality interventions are provided to participants throughout the trial.

**15.4.1** It is recommended that the following components of risk reduction be monitored:

i. Quality of protocols for counselling, STI management, and referral;
ii. Cultural, linguistic, gender and age appropriateness of the counselling for target groups;
iii. Counsellor skills and the degree to which counsellor training corresponds with policy developed by the National Minimum Standards Committee for the Accreditation and Training of HIV/AIDS counsellors;
iv. Procedures by which risk reduction counsellors are selected, trained and supervised;
v. Availability of adequate supplies of barrier methods and risk-reduction materials; and
vi. Risk-reduction interventions should also be evaluated by participant satisfaction, and with regard to their efficacy in reducing high-risk behaviour.

**15.5** In order to reduce a real or perceived conflict of interest, evaluation of consent and risk-reduction measures could be done by, or in collaboration with, an independent agency. Consideration should be given to appointing an independent monitor, or expanding the trial monitor's responsibilities, to evaluate consent and risk-reduction measures. This should take into account protection of participants' confidentiality.

**15.6** Recommendations to evaluate consent and risk-reduction measures supplement the usual guidelines for monitoring HIV vaccine trials for safety and compliance with scientific and ethical standards and regulatory requirements.



## 16. Care and treatment

**Trial participants must be provided with treatment and care for HIV/AIDS and its associated complications if they become HIV infected during the course of an HIV preventive vaccine trial. Sponsors and investigators should ensure that participants have access to a package of high-quality treatment and care that includes antiretroviral therapy (ART). Furthermore, sponsors and investigators should build the capacity of trial-linked health care centres to deliver services to the host community, and ensure that there is a contribution of lasting benefit to host communities. Considerations for sponsors and investigators to ensure access to treatment and care include: taking active steps to promote the welfare of trial participants and to reduce inequities in health care between participants in sponsor and host countries.**

**16.1** Sponsors and investigators must ensure that treatment and care for HIV infection is provided to participants who become HIV-infected during the course of an HIV vaccine trial.

**16.1.1** Treatment and care for HIV-infected participants will require many

components. These include: Ongoing counselling; baseline screening and immune monitoring; preventive methods and means; prevention and treatment of opportunistic infections and common morbidity; treatment for other STIs; tuberculosis prevention and treatment; physician visits; nutrition; palliative care, including pain control and spiritual care; referral to social and community support; family planning; home-based care, and antiretroviral therapy (ART).

**16.2** Critical considerations in determining sponsor/investigator obligations to ensure treatment, and the components of treatment and care that should be assured, are:

i. The context of the trial, including the sponsor-host collaboration, and the resources of the sponsor;
ii. The design of the trial, including whether it is a multinational trial with an arm in a sponsor country;
iii. The active promotion of the welfare of trial participants;
iv. The need to reduce inequities in access to health care for participants from sponsor and host countries;
v. Establishment of a fair distribution of the overall risks and benefits of the research;
vi. The availability or development of mechanisms, or infrastructure, to ensure the provision of treatment components to participants that are not routinely available in South Africa (e.g. ART);
vii. International human rights standards; and
viii. Sound estimations, as judged by known facts or other studies, of the probability and magnitude of potential risks to participants, including:
    - The possibility that participants will have false beliefs about vaccine efficacy and engage in increased high-risk behaviour, and
    - The theoretical possibility that participants who are vaccinated and subsequently exposed to HIV may be more susceptible to infection or disease.



**16.3** In early debate forums held in South Africa consensus was not achieved on the obligations of sponsors, or on the components of an acceptable package of treatment and care, including whether ART should be provided.

**16.3.1** Some consensus existed that trial participants should receive better treatment and care than would be available to them in the current public health care system in South Africa. That is, they should be provided with treatment and care that reflects an improvement over what they would ordinarily obtain. This corresponds with the standard for collaborative international research articulated in *Book 1, 11.4.4 vi.*

**16.3.2** Some argued that sponsors and investigators are obligated to provide, or ensure access to, treatment for HIV infection based on the potential for a false belief in vaccine efficacy, and increased risk behaviour; arguing that the obligation to treat HIV infection rests on compensation for injury related to trial participation. Others argued that sponsors and investigators are obligated to ensure access to treatment based on consid-erations

of distributive justice, and the need to reduce inequities in health care for participants in multinational trials.

**16.4** At a meeting commissioned by the Interim National Health Research Ethics Committee in February 2003[5] there was agreement that:

**16.4.1** Sponsors and investigators should provide, or ensure access to, high-quality treatment and care for participants who become infected during the course of an HIV preventive vaccine trial, including ART (see *Point 16.1.1*).

**16.4.2** Trial participants who become HIV-infected after the end of the trial, or persons who are identified as HIV-infected at screening for participation in a trial, should be referred to existing health care services, with the understanding that there will be progressive implementation of a programme of state-supported ART (see *Point 16.4.9*).

**16.4.3** Trial participants who become infected during the course of a trial, then withdraw from the trial but continue with appropriate follow-up, are eligible for the same treatment and care they would have received had they not withdrawn.

**16.4.4** Prior to the initiation of any trial sponsors should ensure that resources are contributed towards the treatment and care of trial participants.



**16.4.5** Alternatively a national trust fund, and a national mechanism could be established to facilitate provision of treatment and care for HIV infected trial participants.

**16.4.6** Treatment and care for participants who become infected during a trial should be provided according to the South African HIV Clinician's Society Guidelines, until such time that national government guidelines are in place.

**16.4.7** The guidelines for treatment and care for trial participants who become HIV-infected should be regularly reviewed.

**16.4.8** Capacity of trial-linked health care service centres in the host community should be strengthened. That is, the 'local standard of care' in the host community should be improved so that it is provided with a contribution of lasting benefit. Community representatives should play a key role in deter-mining how such capacity is built, to ensure that this is optimally responsive to the health needs and priorities of the participating community.[6] The capacity of community repre-sentatives to participate meaningfully in such deliberations should be actively built (see *Points 3* and *5*).

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[5]The Interim National Health Research Ethics Committee was mandated to set national norms and standards for health research in South Africa.

[6]Benatar, S and Singer, P (2000). A new look at international research ethics. *BMJ 321*: 824-826.

**16.4.9** Provision of high-quality care for HIV infection to trial participants may act as an incentive to participate, and may introduce some inequalities in access to health care. However, provision of high-quality care is considered to reflect active promotion of the welfare and the fair treatment of participants in HIV preventive vaccine trials.

# 17. Women

**Women, including those of child-bearing potential, who are pregnant or breast-feeding, should be recipients of future HIV preventive vaccines. Therefore, women should be included in clinical trials to verify safety, immunogenicity, and efficacy from their standpoint. However, the involvement of such women must be based on a sound risk-benefit analysis, and their informed consent.**

**17.1** In many communities throughout the world women are at high risk of HIV infection. Therefore, the safety, immunogenicity, and efficacy of candidate vaccines should be established for women, and for their fetus and breast-fed child, where applicable. Women, including women of child-bearing potential, pregnant women, and breast-feeding women, are thus eligible for enrolment in HIV preventive vaccine trials. They are also eligible on equity grounds.



**17.2** The enrolment of pregnant and breast-feeding women should take place only:

i. After appropriate studies on less vulnerable participants have been conducted;
ii. If a favourable balance of risks and benefits is established (see *Book 1,7.1.3* and *9.12.4.8*);
iii. With their informed consent (see *Points 12* and *13*). Such participants must be informed of and understand any potential for teratogenesis or other risks to the fetus, and/or the breast-fed infant;
iv. If risk-minimisation measures are undertaken, e.g. if there are risks related to breast-feeding, nutritional substitutes and other supportive services should be made available and participants should be informed of such (see *Points 12* and *13*); and
v. In certain circumstances, recognition should be given to the interests of the father of the fetus to participate in decision-making (see *Book 1, 5.3.1.1.3*).

**17.3** This guidance point must be read in conjunction with *Book 1, 5.3.1.1.3*; and *9.12.4.8*.

# 18. Children

**As children should be recipients of future HIV preventive vaccines, children should be included in clinical trials in order to verify safety, immunogenicity and efficacy from their standpoint. The development of HIV vaccines for children in South Africa must address specific scientific, ethical, and legal considerations relevant to children, so that their welfare is safeguarded and promoted.**

**18.1** The Constitution defines a child as someone younger than 18 years.

**18.2** Children, including infants and adolescents in many communities throughout South Africa, are at high risk of HIV infection. Infants born to HIV-infected mothers may be at risk of becoming infected during birth or during the postpartum period through breast-feeding. Adolescents are also at high risk of infection because of sexual activity, and/or lack of access to HIV prevention means.

**18.2.1** As children are at risk of HIV infection, children stand to benefit from the development of HIV preventive vaccines. Therefore, children should be included in clinical trials in order to verify safety, immunogenicity and efficacy from their standpoint.



**18.2.2** The participation of children in research also honours their right to equal consideration by enabling their access to safe and efficacious products.

**18.3** Before undertaking research in children, investigators must satisfy research ethics committees of the points detailed below[7].

**18.4 The research could not be carried out equally well with less vulnerable participants:** Ethical justification of the involvement of children in research requires that the research would not be equally informative if carried out on less vulnerable participants, and there is a specific need to perform the research on children (see *Book 1, 7.1.3.2*). According to this reasoning, the participation of children in HIV vaccine research should be considered only if their participation is indispensable to establish safety, immunogenicity and efficacy data relevant to children.

**18.5 The purpose of the research is to obtain knowledge relevant to the health needs of children:** Ethical justification for the involvement of children in research requires that the purpose of the research is to obtain knowledge relevant to the health needs of children. That is, the research is intended to obtain knowledge that will lead to the improved prevention or treatment of diseases or health problems characteristic of children, either to actual child participants or children as a class.

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[7]Certain of these provisions on research with children are not entirely consistent with Book 1, which is currently under revision.

**18.6 The risks presented by research interventions are reasonable and justifiable in relation to expected benefits:**

**18.6.1** The risk from research interventions and procedures that *do not* hold out the prospect of direct health-related benefits for the individual participant should be no more likely and no greater than the risk attached to routine medical or psychological examination of children, or the risk that is normally encountered in the daily lives of people in a stable society (see *Book 1, 5.3.1.2.1* and *9.12.4.3.1*).

**18.6.1.1** Slight increases above such risk may be permitted when there is an over-riding scientific or medical rationale. The research should be designed to be responsive to the disease affecting the prospective participants or to conditions to which they are particularly susceptible, and the objective of the research must be sufficiently important to justify exposure of the participants to the increased risk.

**18.6.2** The risks of research interventions or procedures that *do* hold out the prospect of direct health-related benefits should be justified by the anticipated benefit to participants.

**18.6.3** In making these determinations, research ethics committees should consult with experts, including persons with expertise in paediatric and child health.



**18.7 Legal and ethical requirements for informed consent will be met:**

**18.7.1** In South Africa, the Constitution states that no person shall be subject to experimentation without informed consent. Persons above the age of 18 years, who are of sound mind, are generally considered capable of giving inde-pendent informed consent for participation in research (see *Point 12.7*)[8,9]. When persons below the age of 18 are to be involved in research, proxy consent from a parent or legal guardian must be obtained.

**18.7.1.1** Therefore, the enrolment of children in HIV vaccine research in South Africa requires informed consent from a parent or legal guardian, and assent from the child, according to his or her evolving capabilities.

**18.7.2** Because the Child Care Act specifies that South African children who are 14 years and older may give consent to medical treatment of

[8] This is so even while inconsistency prevails in South African law regarding the age at which capacity to consent is presumed to be obtained. Various laws prescribe various ages for individual consent. In terms of the Child Care Act any person over the age of 14 years is competent to consent, without the assistance of parent or guardian, to any medical treatment and a person over the age of 18 years is competent to consent to an operation. In terms of the Human Tissue Act of 1983, a person of 14 years may donate blood; and in terms of the Termination of Pregnancy Act of 1996 a woman, that is a female person of any age, can consent to an abortion.

[9] In South African law, in a few defined circumstances, persons under the age of 18 are considered able to have full legal capacity to give their own consent to participate in research. So called "emancipated minors" include persons under the age of 18 years who are married, widowed or divorced, or who have applied for emancipation and it has been deemed by a court that they are competent to administer their affairs, and that their best interests are served by anticipating majority. As this is a complex and emerging area in the law, legal advice should be sought.

themselves (see *Book 1, 5.3.1.2.1*), such children are considered (by implication) able to give consent to "therapeutic research".

**18.7.2.1** If a research ethics committee classifies an entire HIV vaccine trial protocol as "therapeutic research"[10] it is possible that independent consent for participation could be secured from children who are 14 years and older. However the permission of the parents or legal guardian is still highly desirable. The participation of children who are under 14 years would require parental consent as well as assent from the child according to his or her evolving capabilities.

**18.7.3** If a research ethics committee classifies an entire HIV vaccine trial protocol as "non-therapeutic research", parents must provide proxy consent for participation and the child must assent (according to his or her evolving capabilities), provided that the risks are no more likely and no greater than the risk attached to routine medical or psychological examination of children, or the risk that is normally encountered in the daily lives of people in a stable society (see *Point 18.6.1*). Where there is an over-riding medical or scientific rationale, such risks may be slightly increased (see *Point 18.6.1.1*).



[10] Book 1 classifies whole research protocols as "therapeutic" or "non-therapeutic" research. Therapeutic research is defined as research that aims to investigate an intervention that may be of direct benefit to volunteers. Non-therapeutic research is defined as research that aims to acquire generalizable knowledge that may benefit other persons.

# Useful contact details

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