

## **APPENDIX A: ETHICAL CONSIDERATIONS FOR HIV/AIDS CLINICAL AND EPIDEMIOLOGICAL RESEARCH**

### **PREFACE**

This section emanated from a series of consultations held by the Task Group on Ethical Guidelines for HIV Research. The aim of this document is to provide broad ethical guidelines to address the current challenges posed by HIV and AIDS research, but it is understood that new problems will continue to present themselves. Therefore this section will be continually reviewed and revised as necessary. The particular ethical challenges posed by HIV vaccine research is set out in the guidelines on Ethics for Medical Research: HIV Vaccine Trials (MRC Book 5) which has been approved by the Interim National Health Research Ethics Committee.

### **1. BACKGROUND**

In recent years there has been an increase in HIV-related clinical and epidemiological research. This has included advances in anti-retroviral therapy, which has influenced the clinical course of HIV infection, reduced mother-to-child HIV transmission and HIV transmission following occupational exposure to HIV. HIV vaccine research is now an international priority. HIV-related clinical research includes strategies to prevent HIV infection (through use of vaginal microbicides) and to investigate medications that may increase the risk of HIV infection, such as long-acting progestins. This research often necessitates determining the HIV status of individuals involved in clinical trials.

Clinical and epidemiological research involves complex ethical challenges. These include considerations of access to clinical trials, informed consent, use of medications after the completion of drug trials, drug toxicities, long-term side-effects, the appropriateness of proposed research to South Africa, and the release and publication of the research results.

South Africa is a middle-income country within which there are severe economic disparities; the majority of the population being of a low socio-economic status. South Africa, however, is in many ways an ideal country for clinical and epidemiological HIV-related research. It has a rapidly expanding HIV and AIDS epidemic that is favourable for research studies. The country's well-developed infrastructure offers clinical and scientific expertise, academic institutions of good standing, competent laboratory and clinical facilities and an industrial infrastructure, with high standards in communications and other relevant medical technologies. Information gained from clinical and epidemiological research could have critical implications for South Africa and in the international sphere including in research ethics.

This document attempts to address several ethical issues relating to HIV and AIDS clinical and epidemiological research in South Africa.

With many ethical issues, answers are not always clearly right or wrong. There are, however, several universally accepted ethical principles. These principles should be applied within the context of South Africa, and this document is intended to facilitate a more uniform approach to common ethical issues concerning HIV and AIDS related research.

### **2. SELECTED ISSUES RELATING TO HIV AND AIDS CLINICAL AND EPIDEMIOLOGICAL RESEARCH**

#### **2.1 Research should be appropriate to South Africa**

International research ethical guidelines, including those of the Council for International Organisations of Medical Sciences, emphasise the need for proposed research to undergo ethical and scientific review in both the initiating and host countries. This is to avoid exploitation of participants in the host

country and to ensure sensitivity to the needs of vulnerable communities. Vulnerable communities are defined by UNAIDS as having some or all of the following characteristics:

- Limited economic development;
- Inadequate protection of human rights and discrimination on the basis of HIV antibody status;
- Inadequate cultural experience or understanding of scientific research;
- Limited availability of health care and treatment options;
- Limited ability of individuals in the community to provide informed consent.

As a result of past exploitation and oppression, South Africans are vulnerable to ethical abuses. Care and sensitivity should be applied to prevent exploitation of South Africa's disadvantaged communities.

Research initiated in developed countries, including Phase I and Phase II clinical trials, should not be conducted in South Africa merely because this country can offer better research opportunities. Research conducted in South Africa should be relevant to the health needs of the country.

Research and clinical trials, however, should be conducted within various settings and applied to communities in different social and economic circumstances. Research projects undertaken in South Africa should be carefully evaluated and examined as to their current and future relevance. The science of HIV and AIDS is developing rapidly and proposed interventions, which may seem to be costly and inappropriate at present, may indeed become realistic options in the future.

## **2.2 Research standards**

Vulnerable communities are often characterised by sub-optimal living conditions and poor access to health and social services. This should not lessen the need for high-standard research and use of universally accepted ethical standards. It is imperative that good research and ethical standards be applied in vulnerable and non-vulnerable communities.

## **3. HIV-RELATED DRUG TRIALS**

HIV-related clinical trials not only refer to anti-retroviral drugs but also to trials with medications such as immune modulators, and drugs for the treatment and prevention of HIV-related opportunistic infections.

### **3.1 Access to HIV related medication**

Drug trials are conducted to determine various outcomes such as efficacy, safety, impact on health status of the individual, short and long term side effects, survival benefits, quality of life, adherence to drug regimens, compliance with therapy and comparisons with other therapeutic options.

While anti-retroviral therapy is effective, it is expensive and efforts have been made to make it available in the South African public sector. Participation in drug trials is often the easiest way of gaining access to anti-retroviral therapy. Drug trials should not be conducted solely because they facilitate access to drugs for some patients, although this may often provide benefits to the individual.

The rationale for drug trials should be independently assessed and evaluated on its merits. Researchers must ensure that patients in drug trials provide informed consent and understand the implications of the trial. This includes the advantages and disadvantages of all drug regimens, and the potential limitations in taking medications only for the period of the drug trial.

The ethics committees must consider these advantages and disadvantages to the trial participants and the general community to determine whether such trials are appropriate and relevant in the South African context.

Patient autonomy must be respected. endeavours to promote autonomy should be pursued through seeking opinions of representatives of vulnerable communities, including persons living with HIV and AIDS.

### **3.2 Placebo-controlled trials**

Ethical guidelines that apply to controlled therapeutic trials are generally adequate to protect the rights of HIV-infected persons. A special case involves the use of placebo after an intervention has already been shown to be effective. The general principle is that the use of placebo in these circumstances is unethical. However with increasing disparities in health care between wealthy and poor countries, therapy that has been shown to be effective is often unaffordable in resource-poor settings. This is particularly true of therapeutic advances in HIV infection, which a far bigger health care problem in poor countries in sub-Saharan Africa than in industrialised countries. It may on occasion be justifiable to use placebo in communities that do not have access to interventions that are the standard care in resource-rich settings. However, placebos may only be used when the anticipated benefits will outweigh the risks to participants, and participants will not be harmed, and full justification must be provided for use of placebo.

### **3.3 Adverse drug effects**

Drug trials have the potential to cause short- and long-term ill effects. The patient information section of the informed consent document should specify the action to be taken if the study drug or drugs are withdrawn because of side effects. In such a situation, appropriate therapy to manage the adverse drug effects should be made available within the study framework at no cost to the patient, by referral to the local health service, or through the patient's medical insurance, unless exceptions have been agreed upon by all parties.

### **3.4 Patient management after withdrawal from a study**

Where patients withdraw from a study for any reason, or where a study is completed, the patients should be advised about the ongoing management of their condition. Except in cases where therapeutic efficacy is demonstrated (see below), ongoing therapy should be administered according to the local standard of care. Costs of this care should be borne by the local health service, the patient's medical insurance or the patient.

### **3.5 Access to study medications following the completion of clinical trials**

Many patients who participate in HIV and AIDS treatment trials have no other access to drug therapy. Where a patient shows a therapeutic response to a study drug, that patient should be offered ongoing treatment. In designing studies, consideration should be given to the costs of long-term provision of study drugs and of clinical monitoring, including the costs of medical staff. The duration of drug therapy in a study should also be clearly stated in the patient information section of the informed consent document.

## **4. HIV TESTING**

HIV testing is frequently required in clinical and epidemiological research, including:

- Epidemiological studies, such as sentinel surveillance on pregnant women;
- Observational studies, such as the effect of long-acting progestins on the risk of HIV transmission in women;
- Drug trials, to establish efficacy and safety;
- Vaccine trials.

HIV testing is a complex issue with important implications and consequences to the individual. Informing persons that they are HIV-positive severely affects their quality of life and should be considered to be a major intervention.

#### **4.1 Advantages and disadvantages of knowing one's HIV status**

Selected advantages may include:-

- The opportunity to avail oneself of health care and counselling for HIV, which has many benefits;
- Access to antiretroviral treatment;
- Preventing the transmission of the HIV to sexual partners;
- Informing one's sexual partners;
- Not offering blood for transfusion;
- Preventing mother-to-child HIV transmission.

Selected disadvantages of knowing one's HIV status may include:

- Mental stress, depression and despair;
- Stigmatisation;
- Discrimination;
- Rejection by family, friends and sexual partners.

The advantages and disadvantages of HIV testing should be carefully considered and included in informed consent forms.

#### **4.2 Confidential HIV testing**

In confidential HIV testing, the following criteria should be met:-

- Adequate pre-test counselling;
- Informed consent in the case of children must be obtained from the parent or lawful guardian, as well as from the child if sufficiently mature. Consent to HIV testing should form part of the consent document for research that requires HIV testing.
- Adequate post-testing counselling;
- Referral to an accessible centre for ongoing psychosocial support and basic medical care. The centre should provide care that conforms at least to the national standard of care for HIV prevention and treatment, including the provision of condoms.

#### **4.3 Unlinked anonymous HIV testing**

This form of HIV testing is done for surveillance purposes, such as the National Antenatal Survey and the HIV and AIDS Behavioral Surveillance. It is considered ethically acceptable to conduct unlinked anonymous testing without individual consent if the following criteria are met:

- Blood is routinely collected for a reason other than HIV testing;
- After routine testing, personal identifiers are removed;
- Leftover blood or blood products are used for HIV testing;
- No other non-routine interventions, including the completion of questionnaires, are carried out.

Ideally, confidential HIV testing should be available to individuals in the target population where unlinked HIV testing is conducted. Referring individuals to voluntary counseling and testing centres should be considered.

#### **4.4 Linked anonymous HIV testing**

In linked anonymous testing the HIV result is linked to a patient's other clinical data, but the patient remains anonymous. An independent person randomly assigns code numbers to patients' sera prior to HIV testing. The patients' identities are then removed from the database and the order of patients is changed. The HIV result is added to the database and 'linked' to the other data obtained before being returned to the investigators. This form of testing is best suited to research where HIV infection is a major confounder and not where HIV infection is the endpoint. Patients should provide informed consent to linked anonymous testing and be offered confidential HIV testing (see Confidential HIV testing).

In unlinked anonymous and linked anonymous HIV testing, researchers should not be able to identify, either directly or indirectly, the HIV test results of individuals.

### **5. POPULATION-BASED STUDIES TO PREVENT HIV TRANSMISSION**

These are studies designed to assess the effect of an existing or proposed intervention on the transmission of HIV in a particular population; the effect of long-term use of contraceptives on the risk of acquiring HIV infection, post-sexual-abuse anti-retroviral prophylaxis, or placebo-controlled mother-to-child transmission.

Observational research studies may not provide immediate personal benefits and usually require large numbers of participants. Such studies require active community participation in both design and monitoring if the intervention is to be applied to a population. Consent of community representatives is not a substitute for individual consent.

Where an intervention has been shown to effectively reduce HIV transmission, it should not be withheld from research participants. All participants must be given information and the means to prevent HIV transmission by practising safer sex and effective treatment for sexually transmitted diseases. Any treatment offered should conform at least to the local standard of care.

### **6. INFORMED CONSENT AND INCENTIVES**

Informed consent may be difficult to obtain, especially in disadvantaged and vulnerable communities where literacy and education are inadequate, and where there are language barriers. However, every effort must be made to achieve informed consent despite the challenge of linguistic and cultural barriers.

Incentives for patients to submit to research need careful consideration. Incentives should not be so excessive as to unfairly influence patients to submit themselves to the trial. Incentives relating to financial benefit, transport, and food should be fair and reasonable without 'making the patient an offer they cannot refuse' and thereby influence the patient to overlook other important considerations.

### **7. RESEARCHER ISSUES**

#### **7.1 Incentives**

Pharmaceutical companies conducting research on their products frequently offer incentives to researchers. Researchers should be wary of incentives that may affect their objectivity and neutrality, while seeking to promote excessive allegiance to a particular pharmaceutical company. Researchers and members of ethical committees are required to disclose their financial involvements and other conflicts of interest relating to proposed research projects.

## 7.2 Releasing and publishing research results

In recent years investigators have released preliminary research data prematurely to the Press, with serious and negative consequences. Premature release may result in the broadcast of sensational, inaccurate, misleading and irresponsible information on HIV and AIDS. Unfounded and insupportable claims may mislead the public and create unrealistic expectations. To prevent the creation of unrealistic or misleading expectations the following must be carefully considered:

- Researchers should not communicate the results of clinical trials or of any research to the public without first subjecting the study to peer review and to the normal rigorous scientific scrutiny needed for therapeutic and vaccine trials.
- Phase I and II trials should be published in scientifically refereed journals or be presented to scientific forums where results can be openly viewed and scrutinised.
- Important findings that need to be urgently released, should be released via the ‘fast track’ system employed by most reputable scientific journals. Most medical journals have now developed this system to fast-track review and publish important research findings.

## 7.3 Implementing research findings

Research with direct public-health implications, such as vaccine trials, requires wide consultation. This should include discussions with the South African Department of Health and the Medical Research Council, so that implementation of study results may be addressed at an early stage.

## 7.4 Research ethics committees and field support

Proposals for clinical and epidemiological research should be submitted for approval to relevant local research ethics committees and or to the South African Medicines and Medical Devices Regulatory Authority. Principal researchers or investigators must provide adequate supervision to ensure that ethical considerations are properly observed by their delegated staff.

## 8. HIV VACCINE RESEARCH

There are various international and national vaccine research initiatives in South Africa. This research is highly specialised and raises many ethical issues. This document will not address the range of issues that are being addressed by the appropriate vaccine research groups, including the Guidelines on Ethics for Medical Research: HIV Vaccine Trials (MRC Book 5). Some of the important ethical considerations include:

- The implications of widespread HIV testing on high-risk populations;
- The impact of local HIV prevention initiatives on research outcomes;
- The possible influence of receiving a vaccine candidate on reducing incentives for participants to take necessary precautions to prevent HIV transmission;
- The implications of ‘false positive’ HIV tests in patients who agree to vaccine trials;
- The appropriateness of the vaccine clade to the local population.

Vaccine research should be done in consultation with national and international initiatives.

## 9. INVOLVEMENT OF PEOPLE LIVING WITH HIV/AIDS (PLWHA/PWAs)

The many tensions, dilemmas and ethical considerations surrounding HIV/AIDS-related research necessitate a wide consultative process. PWAs are essential participants in this process and should form part of the consultation from the very early stages of the research process.

## **10. SPECIAL CONSIDERATION TO SPECIFIC SUBGROUPS OF THE SOCIETY**

In addition to vulnerable communities, there are populations that require special consideration. These include women, prisoners, and children.

**10.1** Women should be appropriately considered as research participants unless there are compelling reasons to support their exclusion.

**10.2** In research involving prisoners, researchers should ensure the voluntary nature of the informed consent provided. Ethics committees reviewing research proposals involving prisoners should consider the inclusion of prisoners or prison representatives on such reviews.