

National Policy guidelines on HIV vaccine RESEARCH, DEVELOPMENT AND EVALUATION

DRAFT



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Ministry of Health and Child Welfare

FOREWORD

.....The purpose of this document is to provide guidance to government and non governmental sectors and scientific groups in Zimbabwe working with international regional and national stakeholders and communities in the development and evaluation of candidate vaccines relevant to Zimbabwe. The guidelines are to be used by authorities responsible for the approval, coordination and supervision of candidate vaccine trials in the country. It provides useful resources to members of scientific and review committees as well as national medicines regulatory and biosafety authorities in regulating HIV vaccine trials in Zimbabwe.

CONTENT.....

ACKNOWLEDGEMENT

Members of the HIV Vaccine Working Group

R A Kambarami
J Matenga
G Mahlangu
Chipato
S Mutero

Suggested list of stakeholders to be consulted for input

ORGANISATION	REPRESENTATIVE
Ministry of Health and Child Welfare	Dr Mugurungi Dr Chakanyuka . Mr Chihanga
NAC	Dr Magure
MCAZ	Ms GN Mahlangu
MRCZ	Ms G.N. Mhlangu/Dr Chipato/Mrs Munyati (already part of Committee)
RCZ	Prof Zijenah
ETHICS	Prof Jens Mielke/Rose Chekera
LAWYER	Ask from Faculty of Law through or Ministry of Legal and Parliamentary Affairs
PRIEST	
HEALTH ECONOMIST	Dr Mawera
IMMUNOLOGIST	Prof. E. Gomo
EPIDEMIOLOGIST	Profs. Kambarami/Matenga/ Dr Chipato
PAEDIATRICIAN	Prof Nathoo/Kambarami
SOCIAL SCIENTIST	Mr A Chingono / J. Mutambirwa
People Living with HIV	Edward Mupunga
Collaborating Partners	WHO, UNICEF, CDC, UNESCO, UNAIDS etc
PRIVATE SECTOR	

ACRONYMS

1. BACKGROUND

1.1 The HIV epidemic in Zimbabwe. The current situation of the HIV epidemic in Zimbabwe, and justification for HIV vaccines.

Zimbabwe is reported to have one of the highest HIV/AIDS infection rates in the world. Data from national sentinel surveillance and national and local community based surveys show declining prevalence rates from 32% in 2000 to 22.1% (14.6%- 30.4%) in 2003 to 20.1% (13.3%-27.6%) in 2005 and now to 18.1% in 2006 in the 15-49 year age group. (WHO/UNAIDS 2006)¹. Zimbabwe needs to sustain the declining HIV incidence and prevalence. There is enormous hope in the potential of an HIV vaccine to bring this epidemic under control. For decades, vaccines have proven to be among the most powerful and cost-effective disease prevention tool available e.g. the smallpox and measles vaccines. Vaccines also have a potential advantage of reaching populations that otherwise have limited access to health care and prevention services and they do not depend on consistent and sustained behaviour change by millions of individuals. In this third decade of the HIV pandemic, as the numbers of those infected by HIV and dying from AIDS remain dramatic, the need to find preventive and therapeutic vaccines that work is extremely urgent.

1.2 AIDS impact on development

The AIDS epidemic has had a negative impact on life expectancy in the past three decades, particularly in Zimbabwe. Life expectancy at birth is currently

estimated at 38 years which is about 20 years shorter than before the AIDS epidemic.

The demand for medical care related to HIV infection currently overburdens already fragile health systems, and AIDS exacerbates poverty at household and at country level since the disease affects mainly individuals in the most productive age group, reaping lives and leaving orphans to be cared for by relatives or by the State.

1.3 National response to HIV

Prevention, care and treatment activities in Zimbabwe are coordinated by NAC and implemented by the AIDS and TB Unit of the Ministry of Health and Child Welfare. The responses to the epidemic have included HIV preventive education and behavior change strategies, PMTCT, supply of safe blood and blood products, condom promotion, disease surveillance as well as voluntary counseling and testing and treatment, care and support interventions; measures which are believed to have led to reduction in the prevalence and incidence of HIV in some populations in the country as well as mitigating the impact of the epidemic. However, there is a need for more effective measures to further “control the epidemic”. An effective vaccine against HIV is one intervention that is likely to have the ultimate effect of controlling the epidemic.

The national HIV and AIDS policy for Zimbabwe was developed in 1999 to promote and guide present and future responses to the HIV and AIDS epidemic in Zimbabwe. Unfortunately this policy was silent on HIV vaccines and microbicides as these developments did not exist at the time. The recently reviewed and adopted Zimbabwe National Strategic Framework on HIV and AIDS (2006-2010) is also silent on HIV vaccine and microbicide research. Comprehensive approaches to HIV/AIDS that includes paying attention to the development of new AIDS prevention technologies, including vaccines and microbicides have become important and policy guidelines critical.

In the absence of a cure for HIV and AIDS, the following HIV vaccine policy additions are made:

- a) The government of Zimbabwe is committed to engaging in HIV vaccine trials including vaccine trials for prevention and treatment of HIV and as such,
 - i. Promotes and supports HIV prevention and treatment vaccine clinical trials.
 - ii. promotes and supports the use of HIV vaccines that are safe, efficacious and cost- effective as a prevention or treatment strategy.
- b) Zimbabwe adheres to international goals and principles and supports ongoing regional and international HIV and AIDS vaccine initiatives.

Zimbabwe is a signatory to a number of regional and international conventions which include MDGs, UNGASS, Final communiqué 2003 SADC, The Maseru declaration, SADC Strategic framework on HIV and AIDS and others.

By adopting the UNGASS Declaration of Commitment, governments, among other issues commit themselves to:

- Increase and accelerate research on HIV vaccines.
- Increase research to improve on HIV prevention and therapy, access to prevention, care, treatment, women-controlled methods of prevention, microbicides, and the means to prevent mother-to-child transmission; understanding of the epidemic; and a conducive and ethical environment for research.
- Support the development of research infrastructure, laboratory capacity, surveillance systems, data collection, processing and dissemination, and training of researchers, social scientists, health-care providers and technicians, particularly in countries most affected by, or at high risk of, HIV/AIDS.

1.4 Impact of HIV vaccine in Zimbabwe

Data on the epidemiological impact of HIV vaccines are scanty and those that exist are based on mathematical models based on adult data and in situations where vaccines are used for prevention not therapy. The epidemiological impact

of HIV vaccine will depend on the context in which it is used, the characteristics of the vaccine, the strategy of administration and how people respond to it use. In a multisite study using data from Zimbabwe, Uganda and Thailand (1), it was shown that for a vaccine that was 50% efficacious, with 10 years protection and 65% coverage, the incidence of HIV would be reduced by 25% in Zimbabwe in adults 15-49 years of age. It is also known that the type of protection (degree or take) could make a large difference to the impact. On further analyzing Zimbabwean data with respect to type of protection, it was shown that using a vaccine with 50% efficacy, after 5 years, with 65% coverage, HIV incidence would be 32% lower than without the vaccine using either take or degree protection. This is a huge impact if it can be achieved in real life. On further modeling using vaccines of different levels of efficacy, it was shown that at 95% efficacy, vaccine programs can nearly extinguish the epidemic in Zimbabwe. Clearly the model showed that the better the efficacy the higher the impact.

The duration of protection conferred by the vaccine is also of importance. The longer the protection, the higher the impact data showed. However the strategy of revaccination may increase costs but has the same impact as vaccines with long duration of protection. Thus it would appear that a vaccine that is highly efficacious, with life long protection and with wide coverage and given to adults would have a major impact on childhood HIV infection rates since the 99% of paediatric HIV infection is acquired from mother to baby in our population. A vaccine of low efficacy, short duration of protection will have no impact and would give false assurance and even increase risky behaviours,

The need to study HIV vaccines for both prevention and therapy remain paramount and urgent. The 2003 HIV estimates show that there 165000 infected children, 40000 new infections and 36000 deaths. Infant mortality rates have risen from 50 per 1000 live births in the early 1990s to 130 deaths per 1000 in 2003. This calls for studies using innovative interventions that show potential to turn around the epidemic and vaccine trials look most promising. A safe, effective and affordable vaccine that can both increase CD cell count and reduce viral load will show great therapeutic impact and improve survival particularly in resource poor countries.

Ref J Stover et al.

The epidemiological impact of an HIV/AIDS vaccine in developing countries.

Sponsored by the European Commission and World Bank.

2. CHALLENGES INVOLVED IN DEVELOPING AN HIV VACCINE

The development of a safe and effective vaccine against HIV infection involves several challenges. The ideal vaccine should stimulate immunological responses capable of blocking the sexual, injecting and vertical transmission of HIV infection. It must also be able to produce not only antibodies capable of neutralizing free viral particles but also immunological cell responses able to destroy HIV infected cells. There is the additional challenge involved in our not knowing the correlates of immunity to enable us to define what to expect from an effective vaccine. In addition,

based on our present knowledge, it is possible that several vaccines (or true “cocktails”) are required to deal with the various HIV subtypes prevalent in the different countries affected by the epidemic.

In spite of these difficulties, the scientific community is reservedly optimistic concerning the possibility of developing one or more vaccines with varying levels of effectiveness against HIV. This optimism is based on several facts, including:

- a) the existence of individuals who are repeatedly exposed to HIV, do not become infected and develop immunological responses which might explain this resistance; others probably do not become infected because of the lack or changes in the receptors required for HIV entry in the cells;
- b) the existence of vaccine products that protect monkeys from the infection or from developing the disease ;
- c) some vaccine products have triggered potent immunological reactions in human volunteers;
- d) the successful development of other vaccines against several viruses (e.g., hepatitis, poliomyelitis, mumps) even when the understanding of pathophysiology was smaller than in the case of HIV infection.

Vaccine candidates and need for involvement in HIV research, development and evaluation

There are three different types (and purposes) of vaccine candidate products being developed and evaluated:

1. Preventive vaccines: to prevent HIV infection (sterilizing immunity) or the progress towards AIDS (partial immunity);

2. Therapeutic vaccines or active immunotherapy: to prevent or delay the progression of the disease, to decrease the viral load in HIV-infected individuals and to decrease the transmission of HIV infection from infected individuals to their contacts;

3. Perinatal vaccines: to prevent the progression of the disease in HIV-infected pregnant women and the transmission of the viral infection to their children.

There is a growing optimism in the international scientific community concerning the possibility of developing safe and effective preventive vaccines. However, despite the progress in recent years, the correlates of immunity associated with protection are still not well established hence the need for further research.

Viruses isolated from different patients, and specially from different geographic regions, show considerable genetic and thus antigenic variations, which may be a limiting factor to the development of a universal vaccine hence the need for country level involvement in HIV research.

It is important to know whether the HIV-1 strains circulating in the country where the vaccine might be used in the future are sufficiently related to the vaccine prototype being tested. In order to obtain this type of information, it is necessary to keep an HIV molecular surveillance program in the country, systematically collecting blood samples for HIV isolation and its biological, genetic and antigenic characterization.

Results on HIV vaccine to date are encouraging, the trials of immunotherapy or post infection immunization need to be expanded and deepened in order to allow a better assessment not only of the immunological response but also of the clinical and virological parameters, including the effect on HIV transmission, development of AIDS and time of survival.

3. GOALS OF AN AIDS VACCINE

Primarily, the goal of vaccines is to prime the immune system to recognize and protect against a disease caused by a virus or other infectious agent. To have a significant public health impact on the AIDS pandemic a vaccine must be both effective against the wide diversity of global HIV isolates and useful in the developing world, where the need is greatest.

The second potential goal is to significantly suppress viral load and slow the progression to AIDS in vaccines if they become infected by HIV.

It is important to note that while developing an AIDS vaccine that meets the goals outlined above is a scientific challenge, the resources required to do so—funding, technical, and human resources—will only be available if political will supports it. An enabling political environment is necessary to provide the mobilization of resources required to conquer this pandemic.

4. VACCINE EVALUATION PROCESS

Before an HIV vaccine candidate product is evaluated in human subjects, trials to determine the vaccine safety, toxicity and immunogenicity are conducted in small animals and later in non-human primates. After these pre-clinical phases, and if the vaccine products are safe and capable of stimulating the immunological system, they can enter the human phase of clinical trials. Phase I and Phase II trials of safety and immunogenicity of vaccine candidate products are usually conducted in approximately 40 to 200 human volunteers, and the effectiveness in human subjects is determined in Phase III studies, randomized and with appropriate controls, carried

out in thousands of volunteers. The following presents a summary of the development of clinical trials with vaccine candidate products.

Development of Vaccine Candidate Products

Pre-clinical phase: The safety and immunogenicity of the vaccine product are evaluated in

animal trials. This phase must always precede clinical trials in human subjects.

Clinical phase: Clinical trials will determine the safety, immunogenicity and eventually the

effectiveness of the product tested. There are three mandatory phases before a vaccine is licensed by the relevant health authorities:

□Phase I:

Initial trials of safety (innocuity), immunogenicity and dosing in a limited number of volunteers

(10 to 30 individuals). These studies usually involve healthy adults at low risk for HIV infection, for periods varying between 6 months and one year;

□Phase II:

Continuation of the safety and immunogenicity trials The vaccine capacity to stimulate certain immunological responses which might indicate possible protection is evaluated in a larger (around 200) number of individuals. Different doses and schedules are tested, as well as different adjuvants. This phase can last from 6 to 24 months;

□Phase III:

In the third and last phase before the possible license for marketing, the efficacy of the vaccine product is tested in a large number of volunteers (thousands of subjects). The number of volunteers will vary inversely to the incidence of infection and/or the expected

efficacy of the vaccine product. The smaller the incidence of infection and/or the smaller the expected efficacy of the vaccine product, the larger the number of volunteers required. The efficacy is measured by comparing the rates of infection of individuals who received the product and those who received placebo. These trials last from 3 to 5 years and are very expensive. A high level of efficacy in Phase III does not guarantee effectiveness in controlling the epidemic.

This must be assessed under the normal working conditions of the health system, which are different from the special conditions in which the effectiveness trials (Phase III) are conducted, when healthy volunteers are selected and receive the vaccine product or the placebo under highly controlled conditions. Effectiveness (Phase IV trial) depends on the coverage, which is associated with the price of the products and the level of organization of the health services (this level of trials assess the real life situation).

5. THE ETHICS OF HIV VACCINE RESEARCH

It is critical to ensure the integrity of the human subjects of scientific research. Thus, the bodies responsible for clinical trials with HIV vaccine products in Zimbabwe must provide the best treatment proved anywhere in the world to those volunteers who may eventually become infected by HIV, ensure the safety and the protection of the human rights of the human subjects participating in research trials. All protocols pertaining to HIV vaccine research involving human subjects will be evaluated and guarantee human subject protection. The proposal should be reviewed and approved by the following bodies:

1. **Research Council of Zimbabwe** – whose role is to monitor and supervise potentially harmful research. This board also approves

clinical research pertaining to recombinant DNA products and export of biohazardous specimens.

2. **Medical Council of Zimbabwe** whose role is
 - a. to provide technical guidance, advise and decision (approval/disapproval) of specific research protocols intended to be conducted in Zimbabwe in terms of research methodological and ethical issues
 - b. to provide ethical guidance and advise on research programs undertaken within Zimbabwe
3. **Medicines Control Authority of Zimbabwe** whose role is:
 - a. to review proposals on clinical trials that use drugs or medical devices in terms of safety and regulatory compliance issues
 - b. testing study products
 - c. to give approval for clinical trial to be undertaken
 - d. to facilitate importation of study product.
4. **Institutional ethical review committees** whose role is to provide ethical review and guidance at institutional level.
5. **Committee of the HIV and AIDS vaccine trials in the AIDS and TB Unit of Ministry of Health and Child Welfare (to be formed)** whose role will be:
 - Identification of national HIV vaccine research priorities;
 - Evaluation of research proposals;
 - Technically make recommendations on adaptation of the infrastructure, including training where possible; and

- Ensure compliance with the international ethical requirements
- Approval of information and communication on HIV vaccine trials in Zimbabwe.
- Advise on populations suitable for clinical evaluation of HIV/AIDS vaccines.
- Build national consensus on a comprehensive, well-coordinated, long-term strategy for developing and evaluating safe, efficacious and affordable preventive, therapeutic and perinatal HIV/AIDS vaccines.
- Develop and provide a framework for regulatory approval of research trials, manufacture and licensing of HIV/AIDS vaccines and vaccine products in collaboration with relevant departments.
- Provide guidelines for scientific and ethical review of protocols for HIV/AIDS vaccine trials.
- Interact with other ministries and national research agencies;
- Interact with international agencies and the pharmaceutical industry.
- Provide guidelines for monitoring the conduct of HIV/AIDS vaccine trials according to scientifically and ethically acceptable standards.
- Suggest ways and means of ensuring availability, accessibility and affordability of efficacious HIV/AIDS vaccines
- Suggest ways and means of building local infrastructure and the transfer of knowledge and technology on HIV and AIDS vaccines.

6. GOALS AND OBJECTIVES

To promote ethical research, development, production and evaluation of suitable HIV/ AIDS vaccines and ensure sufficient availability of the vaccine for the country through strategic planning and national, regional and international collaboration.

To facilitate research and development of vaccines that can either prevent HIV infection (preventive) or delay progression of disease (therapeutic).

7. GENERAL GUIDING PRINCIPALS OF HIV VACCINE-RELATED TRIALS

Political support is critically important for the research and development of HIV/AIDS vaccines. It is needed to create an enabling environment for researchers, research partners, funding agencies and research institutions as well as volunteers and study communities.

One purpose of setting national vaccine guidelines is to involve leaders at all levels, including government officials, parliamentarians, administrators and community leaders. Women and youth leaders need to be involved at all these levels. The guidelines promote involvement and consultation with other stakeholders including, but not limited to, people living with HIV/AIDSs, lawyers, journalists, health professionals, faith-based organisations and activists.

The guidelines recognize the various economic, social and cultural situations that may affect HIV/AIDS vaccine research and outline appropriate measures to create an enabling legal and ethical environment.

People have the right to be protected from harm and exploitation, and to make their own decisions regarding how they will participate in HIV/AIDS vaccine research. They must therefore be informed about vaccine research and about the risks and benefits resulting from it. The rights and responsibilities of vaccine volunteers must be formally recognized and safeguarded. No person should be stigmatized or discriminated against during the vaccine research process.

1. Guiding principal 1: Vaccine development: Given the severity of the HIV and AIDS epidemic on human, public health, social and economic terms, sufficient capacity and incentives should be developed to foster the early and ethical development of effective HIV vaccines at country level in collaboration with sponsors and partners.

- Include vaccine development in national HIV prevention and treatment and control plans;
- Assess capacity to participate in HIV vaccine development activities nationally, regionally and internationally including identification of resources, partnerships, strengthening scientific and ethical sectors capacity and involvement in clinical trials and conducting readiness studies and campaigns;
- Identify and collaborate with donors, international agencies, funding sources, to make vaccines a reality and sustainable;

- All studies should be conducted by a team of researchers with multidisciplinary knowledge and experience. The Zimbabwean institution to which the main researcher is affiliated must be responsible for the trial;

2. **Guiding principal 2:** Vaccine availability:

Any HIV preventive or therapeutic vaccine demonstrated to be safe and effective should be made available as soon as possible to all participants of the trial in which it was tested as well as other at risk groups.

- Parties directly concerned should begin the discussion before the trials begin. This discussion should include stakeholders such as Ministry of Health, Local Authorities, scientific and ethical groups, NGOs, PLWHA and community representatives.

3. **Guiding Principal 3:** Capacity building. Strategies should be implemented to build capacity in Zimbabwe and in communities to ensure meaningful self determination in vaccine development, ethical and scientific conduct of vaccine trials and allow Zimbabwe to function as an equal partner with sponsor countries in the collaborative process.

- Develop capacity and capability to make decisions regarding nature and participation in vaccine trials as well as being able to identify factors that increase vulnerability to exploitation of communities
- Study sponsors should ensure their full support to the institutions involved in the HIV vaccine trials to develop the research potential required by the trial, including training of personnel, logistic support and infrastructure;.

4. **Guiding principal 4:** Research protocols and study populations. In order to conduct research in an ethically acceptable manner, the research protocol should be scientifically appropriate and the desired research outcome should potentially benefit the population from which research participants are drawn.
- In order to be ethical, clinical vaccine trials should be based on scientifically valid research protocols and the scientific question should be rigorously formulated and capable of providing valid and reliable responses.
 - Protocols should justify the selection of the research population, outline how risks taken by the population are balanced by benefits in that population, address the particular needs of the research population and establish safeguards for the protection of research participants from potential harm arising from the research.
5. **Guiding Principal 5:** Community participation. To ensure the ethical and scientific quality of the proposed research, its relevance to the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation and distribution of results of HIV vaccine research.
- The orientation and community involvement should be one of the partnerships towards mutual education and consensus building regarding all aspects of the vaccine development programme.
 - There should be establishment of a continued forum of communication and problem solving on all aspects of the vaccine development programme from phase 1 to phase 111 trials and beyond.

- Community representation must be present in committees charged with review, approval and monitoring of HIV vaccine research.
6. **Guiding principal 6:** Scientific and ethical review. HIV preventive and treatment trials should only be carried out in communities that have the capacity to conduct appropriate, independent and competent scientific and ethical reviews
- Proposed HIV vaccine research protocols should be reviewed by ethical review committees that include the community where the research is proposed to be taken.
 - Where capacity does not exist, the sponsor should be responsible for ensuring adequate structures are developed for scientific and ethical review prior to the start of the research.
7. **Guiding principal 7:** Vulnerable populations. Where relevant, the research protocol should describe the social context of the proposed research population that create conditions for possible exploitation and create vulnerability among potential research participants, as well as the the steps that will be taken to overcome these and protect the dignity, safety and welfare of participants.
- The following may increase vulnerability and the nature and level of risk of harm to participants and should be considered;
 - i. Government, institutional or social stigmatization and discrimination on the basis of HIV status
 - ii. Inadequate ability to protect HIV related human rights

- iii. Social and legal marginalization of groups from which participants are drawn e.g. sex workers
- iv. Limited availability, access and sustainability of health care and treatment options
- v. Limited ability of individuals or groups to understand the research process
- vi. Limited ability of participants to freely give informed consent on account of gender, illiteracy and other social and legal factors
- vii. Lack of a meaningful national or local ethical review

8. **Guiding principal 8:** Clinical trials. As phases 1, 11, and 111 in the clinical trials development of a prevention or treatment vaccine, all have their particular scientific requirements and specific ethical challenges, the choice of study population for each trial phase should be justified in advance in both 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 populations that are less vulnerable to harm and exploitation.

- Experimental HIV vaccine should be directed towards a viral strain that exists in country
- Establishing a vaccine development programme that entails the conduct of some, most or all of its clinical trial components in a community that is relatively vulnerable to harm or exploitation is ethically justified if:
 - i. The vaccine is anticipated to be effective against a strain of HIV that is an important public health problem in the country

ii. All the other conditions for ethical justification as set forth in this document are satisfied

9. **Guiding principal 9.** Potential harm. The nature, magnitude and probability of potential harm resulting from the participation in an HIV prevention vaccine trial should be specified in a research protocol fully as well as the modalities by which to address these, including provision of the highest standard of care to participants who experience adverse reaction to vaccine, compensation for injury and referral for psychosocial and legal support as necessary.

10. **Guiding principal 10:** Benefits. The research protocol should outline the benefits that persons participating in HIV vaccine research experiences as a result of their participation. Care should be taken so that these are not presented in a way that unduly influences freedom of choice in participation.

At a minimum participants should:

- Have regular supportive contact with health care workers and counselors throughout the course of the trial
- Receive comprehensive information regarding HIV transmission and HIV prevention
- Receive access to HIV prevention methods including male and female condoms
- Have access to a prepaid care and treatment package for HIV and AIDS if they become infected while enrolled in the trial
- receive compensation for the time, travel and inconvenience of participating in a trial

- If the vaccine is effective participants should have the opportunity to develop protective immunity to HIV
11. **Guiding principal 11:** Control group. As long as there is no known effective HIV vaccine, a placebo controlled arm should be considered ethically acceptable in a phase 111 trail.
 12. **Guiding principal 12:** Informed consent. Independent and informed consent based on complete, accurate and appropriately conveyed and understood information should be obtained from each individual while being screened for eligibility for participation in an HIV prevention or treatment vaccine trial and before enrolment.
 - A process of consultation will be used to design an effective informed consent strategy and process. Issues such as literacy, language cultural barriers and decreased personal automatism should be addressed
 - The use of free and informed consent is of foremost importance.
 - Consent should be obtained by a trained professional in an environment that respects the dignity of each individual. The wording of the consent should be understandable, taking into account the participants' language, culture and circumstances;.
 13. **Guiding principal 13:**Informed consent-special measures. Special measures should be taken to protect persons who may be limited in their ability to provide informed consent due to their social and legal status. The following persons or groups should be given special consideration with regards to their ability to provide informed consent in HIV vaccine trails

- People who are minor or subordinate e.g. students, armed forces, refugees, prisoners
 - Individuals who engage in illegal, socially unacceptable and stigmatizing activities e.g. prostitutes
 - Poor people and those dependent on social welfare programmes
 - Women from cultures where their autonomy is not sufficiently recognised
14. **Guiding principal 14:** Risk reduction interventions. Appropriate risk reduction counselling and access to preventive methods should be provided to all vaccine trial participants
- All vaccine trial participants should receive comprehensive counselling concerning methods of reducing risk to HIV transmission
15. **Guiding principal 15:** Care and treatment. Best proven care and treatment attainable in host and sponsor countries for HIV and AIDS and associated complications should be provided to the participants in HIV vaccine trials. A comprehensive care and treatment package should be agreed upon prior to initiating the trial.
16. **Guiding principal 16:** Infants, children and adolescents should be included in HIV vaccine trials in order to verify safety, immunogenicity and efficacy from their stand point. Efforts should be taken to design HIV vaccine development programmes that address the particular ethical and legal considerations relevant to infants, children and adolescents and safeguard their rights and welfare during participation.
17. **Guiding principal 17:** Women. Women, including those who are potentially pregnant, pregnant or breastfeeding should be recipients of future HIV

vaccine. Women should be included in clinical trials to verify safety, immunogenicity and efficacy from their stand point. During such research, women should research adequate information to make informed choices about risks to themselves as well as their foetus and breastfeeding infant where applicable.

- Women, including pregnant and breastfeeding women should be eligible for involvement in HIV vaccine trial both as a matter of equity and because women are more at risk of HIV infection

18. **Guiding principal 18:** Vaccine candidates. All HIV vaccine candidate products to be tested must first be approved in safety and immunogenicity trials in animal models. An evaluation trial with human subjects must comply with the Zimbabwean IRB ;
19. **Guiding principal 19:** Research of HIV vaccines may involve Phase I (safety), Phase II (immunogenicity) or Phase III (effectiveness) trials. If the study proposed is on safety or immunogenicity, the protocol should include a plan for future effectiveness studies;
20. **Guiding principal 20:** Before starting the study, the laboratory markers to be used to distinguish between natural HIV infection and the immune response to the vaccine product should be determined;
21. **Guiding principal 21:** If the candidate HIV vaccine was developed abroad, all the researchers, both from the country of origin and Zimbabwe, should collaborate in all the stages of the study, from the development of protocols to the diffusion of data;

22. **Guiding principal 22:** The study protocol should include written guarantees that the manufacturer will provide sufficient amounts of vaccine, free of charge, for the duration of the study. If the proposed study is on safety and/or immunogenicity, in addition to plans for efficacy studies there should be a written assurance that the manufacturer will provide sufficient amounts of the vaccine, free of charge, for all the studies proposed. If the candidate product is shown to be efficient, should must be an assurance of its free provision to all study participants, for as long as required to ensure its immunizing activity;
23. **Guiding principal 23:** There should be a written guarantee that, if the vaccine candidate product under study proves to be efficient and adequate for large-scale public use, including strain-specific, if indicated, the manufacturer will provide this vaccine to Zimbabwe at special prices within an appropriate period;
24. **Guiding principal 24:** There should be previous agreement that if the volunteers suffer any complication or injury secondary to the vaccine product the sponsor will be responsible for their treatment and rehabilitation. Volunteers must have guaranteed access to the best proven preventive and therapeutic care. There must be agreements with hospitals or health care institutions for the provision of the required medical and rehabilitation services;
25. **Guiding principal 25:** A monitoring system for long-term side effects in the volunteers must be set up and volunteers must be followed for at least 5 years after the end of the trial;
26. **Guiding principal 26:** 14. All HIV/AIDS vaccine studies must be assessed and monitored by the National HIV Vaccine Committee;

27. **Guiding principal 27:** The protocols submitted to evaluation must comply with all the local MOH /National HIV vaccine committee RCZ, MRCZ, MCAZ, Institutional review boards .

GUIDELINES FOR THE SUBMISSION AND EVALUATION OF PROPOSALS AND PROTOCOLS

HIV vaccine-related research proposals and protocols must be submitted to the MRCZ , MCAZ, Vaccine Committee and the AIDS and TB Unit before they are implemented. These bodies must verify that the vaccine protocols comply with the national HIV vaccine policy guidelines, evaluate their technical, scientific and ethical aspects as well as register and assess priority ranking and relevance.

Terms of reference for a science and ethics committee

- Safeguard the dignity, rights, safety and well-being of research participants.
- Provide independent, competent and timely review of the research and ethics of proposed studies, in accordance with national guidelines.
- Verify ethical integrity of HIV/AIDS vaccine trial protocols in accordance with internationally accepted ethical guidelines, such as:
 - Declaration of Helsinki
 - Council for International Organization of Medical Sciences (CIOMS) publication: International Ethical Guidelines for Biomedical Research Involving Human Subjects
 - World Health Organization (WHO) pamphlet: Proposed International Guidelines for

Biomedical Research Involving Human Subjects

– WHO and International Conference on Harmonization Guidelines for GCP, GMP, Good Clinical and Laboratory Practice (GCLP)

– UNAIDS guidance document: Ethical considerations in HIV Preventive Vaccine Research

– Any other relevant or applicable internationally accepted documents that may come

into force hereinafter

• Review research proposals and their supporting documents with emphasis on:

– Scientific design, objectives, statistics and methods

– Storage, disposal and repository of biological materials

– Recruitment of participants

– Care and protection of participants

– Maintenance of confidentiality

– Informed consent process

– Vulnerable groups

– Community considerations

• Monitor ethical adherence through:

– Regularly reviewing the principal investigator's adherence to approved protocol and other aspects of the implementation of the HIV/AIDS vaccine trial

– Supervising interim reports through systematic analysis

– Appointing a committee to supervise the vaccine trial

• Receive and review reports from an independent monitor appointed by the sponsor

• Receive and review reports from the investigator regarding:

– Protocol amendments, deviations and violations

- Serious and unexpected adverse events
- Periodic and final reports
- New information that may affect risk-to-benefit ratio
- Receive and consider recommendations from the Data and Safety Monitoring Board (DSMB) and where necessary, make recommendations to the DSMB.
- Work closely with the WHO ethical review committee, the WHO-UNAIDS Vaccine Advisory Committee and other relevant bodies on HIV/AIDS vaccine research and development.

Data safety and monitoring board (DSMB) (identified by MRCZ for each trial)

In each trial, the establishment of a data safety and monitoring board (DSMB) to evaluate data from HIV vaccine research studies conducted in Zimbabwe is mandatory.

These boards should be multidisciplinary, with the participation of individuals unrelated to the study, the researchers or the sponsors. For international multi centre trials, there is the additional recommendation to establish an international DSMB, with appropriate representation from research institutions and national and international regulatory agencies.

The DSMB should be multidisciplinary with appropriate representation from all scientific disciplines needed to interpret the data and ensure patient safety, including:

- Clinical trial experts
- Biostatisticians
- Bioethicists

- Clinicians knowledgeable in HIV/AIDS
- Epidemiologists
- Virologists
- Immunologists
- Social and behavioural scientists
- Community representatives

Terms of reference for the Data and Safety Monitoring Board

The DSMB will:

- Review the research protocol and the plans for data and safety monitoring.
- Receive and review regular periodic progress reports from the investigators.
- Have access to and review all data generated from the trial for quality and integrity.
- Monitor data regarding safety (adverse reactions), immunogenicity and efficacy.
- Receive and review unblinded results of interim analyses to determine continuation or termination of the trial.
- Evaluate trial progress, including:
 - periodic assessments of data quality and timeliness
 - participant recruitment, accrual and retention
 - participant risk versus benefit
 - performance of trial sites
 - other factors that can affect study outcome such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study
- Give recommendations to the sponsor, IRB, and investigators concerning

continuation or conclusion of the trial(s).

- Ensure confidentiality of trial data and monitoring results.

Other monitoring agencies

Multidisciplinary community advisory board (CAB)

In each trial, the implementation of multidisciplinary community advisory and follow-up board is recommended. These boards should participate in the research process, especially in the community sensitization, ethical aspects and the human rights of the volunteers. They must be independent both from researchers and sponsors.

Selection of vaccine candidate products

The National HIV Vaccine Committee, together with the MCAZ, will review all preclinical data and previous results of trials involving human subjects and recommend (or not) a vaccine product for evaluation. The decision will be based on the research's relevance for the country, the evidence of safety and immunogenicity, on the report of the vaccine antigen with the HIV strains circulating in the country and on the potential effectiveness.

Setting up and maintaining cohorts

In order to assess the incidence of HIV infection, for behavioral studies, counseling and discussion about free and informed participation in vaccine candidate products trials, cohorts epidemiologically compatible with the research objectives should be set up.

Virological and immunological studies and the development and production of supplies and vaccines

Specific projects in the different areas involved should be formulated, not only for developing clinical trials but also particularly for the transfer of technology, with local research and production of supplies and of the vaccine candidates themselves.

The position of the MINISTRY OF HEALTH is that:

1. All efforts should be combined to prevent the greater dissemination of HIV infection, to continue prevention activities, to propagate appeals for solidarity and nondiscrimination, to provide treatment against the virus and opportunistic infections and to carry out research on new drugs and vaccines;
2. In international projects, all researchers involved must collaborate in all steps of the trials, from the planning of the protocols to the utilization of the results obtained;
3. The different Phase I/II trials conducted in the countries of origin may be repeated in Zimbabwe whenever deemed convenient. This is justified by possible differences in immunological responses and side effects due to factors such as nutritional status, different viral strains, and presence of other infections and/or genetic differences in the different populations. Repeated or parallel Phase I/II studies will also contribute to staff training and institutional strengthening;
4. Research projects must include training at all levels, not only related to the specific research. This includes support to infrastructure and improvement of research conditions;

5. Decisions on the types of vaccines to be evaluated, the final research planning, the identification of sites and respective institutions, and all other elements inherent to the conduction of clinical trials related to HIV vaccines in Zimbabwe shall be based on strict internationally accepted ethical and scientific criteria.