HIV vaccine research – South Africa's ethical-legal framework and its ability to promote the welfare of trial participants

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An effective ethical-legal framework for the conduct of research is critical. We describe five essential components of such a system, review the extent to which these components have been realised in South Africa, present brief implications for the ethical conduct of clinical trials of HIV vaccines in South Africa and make recommendations. The components of an effective ethical-legal system that we propose are the existence of scientific ethical and policy-making structures that regulate research; research ethics committees (RECs) that ethically review research; national ethical guidelines and standards; laws protecting research participants; and mechanisms to enforce and monitor legal rights and ethical standards. We conclude that the ethical-legal framework has, for the most part, the necessary institutions, and certain necessary guidelines but does not have many of the laws needed to protect and promote the rights of persons participating in research, including HIV vaccine trials. Recommendations made include advocacy measures to finalise and implement legislation, development of regulations, analysis and comparison of ethical guidelines, and the development of measures to monitor ethical-legal rights at trial sites.

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The HIV epidemic has been described as South Africa's 'greatest threat to public health'.[1] This not surprising given estimates that in 2004 between 4.68 and 7.03 million South Africans were infected with HIV.[2] In this context there is an urgent need to expand current responses to the HIV epidemic, including the development of preventive HIV vaccines. This has been recognised by the Department of Health (DOH) which has prioritised research into vaccines (clade C) as goal number 10 in their 5-year HIV/AIDS Strategic Plan (2000 - 2005). Currently, three HIV vaccine phase I trials are underway in South Africa[3] and more are planned.

The testing of HIV vaccines is ethically complex because, among other factors, such trials involve international collaborations, potentially vulnerable communities and participants, and high levels of discrimination and stigma surrounding HIV.[4] HIV vaccine testing also raises significant human rights issues. Tension exists between public health needs for accelerated work towards HIV vaccines and the individual rights and interests of trial participants. Substantive and procedural ethical-legal safeguards must be ensured for research participants, while such critical research is facilitated.

International ethical guidelines developed by UNAIDS, *Ethical Considerations in HIV Preventative Vaccine Research*,[5] state that these trials should only be carried out in countries and communities that have the capacity to conduct appropriate independent and competent scientific and ethical review. Since the publication of the Nuremberg Code[6] in 1947 and the subsequent Declaration of Helsinki[7] in 1964 it has been recognised that research should be regulated by some type of ethical-legal framework.[8] The nature and extent of regulation varies from country to country.[9] We posit that effective ethical-legal systems have the following fundamental characteristics: (*i*) scientific ethical and policy-making structures that regulate research; (*ii*) research ethics committees (RECs) that review research; (*iii*) national ethical guidelines and standards; (*iv*) laws protecting research participants; and (*v*) mechanisms to enforce and monitor legal rights and ethical standards.[10]

An evaluation of South Africa's ethical-legal framework for research

Structures should exist to approve new medical products, set national ethical standards, and develop research policy

An effective ethical-legal system should have national regulatory bodies including a scientific regulatory structure, a national ethics structure to ensure the ethical conduct of research and a policy-making body to set a locally relevant research agenda.

Prior to the promulgation of the National Health Act*[1] the statutory regulation of research occurred primarily through a scientific body, namely the Medicines Control Council (MCC).

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*Most of the National Health Act was operationalised on 2 May 2005 (*Goverment Gazette* 27503, 18 April 2005). Certain specified sections, including s 71 dealing with the participation of human subjects in reseach, will be implemented at a later date.

The MCC is entrusted with regulating the registration of medicines intended for use on humans or animals and, accordingly, approving any research that will lead towards registration of a product.[12] One of the statutory obligations placed on the MCC is that it must ensure 'that clinical trial protocols are being assessed according to prescribed ethical and professional criteria and defined standards'.[12] The MCC cannot, therefore, authorise research that has not been reviewed in accordance with accepted ethical norms and standards. It appears that this provision places a procedural rather than a substantive obligation on the MCC to ensure that an independent REC has given due consideration to a protocol. However, the role of the MCC with regard to substantive ethical issues is not clear. Although its statutory obligations appear procedural in nature, the MCC has begun to focus on substantive ethical issues. For example, it has begun developing its own guidelines on HIV vaccine research, including ethical issues (personal communication with Mr Thomas Smit, South African AIDS Vaccine Initiative (SAAVI), 27 January 2004). The MCC has also proposed ethical requirements for HIV vaccine trial protocols; for example, it has required that phase I trial participants have 12 years of education (personal communication with Dr Efthyhia Vardas, 5 February 2004). Recently the independence of the MCC has been questioned.[13]

The recently implemented National Health Act supplements the existing, largely scientific regulation of research with additional layers of ethical and policy controls. It allows for the establishment of a National Health Research Ethics Council (NHREC) and a National Health Research Committee (NHRC). Prior to the National Health Act being implemented, an interim NHREC and an interim NHRC were formed.

In terms of section 72(6) of the National Health Act, the NHREC will be mandated to do the following: establish guidelines for the functioning of health RECs, register and audit these, set norms and standards for research, adjudicate complaints about the functioning of health RECs, and institute disciplinary action against those who violate norms or guidelines for research in terms of the Act. The NHRC established in terms of section 69 of the National Health Act is a policy-formulating body that advises the Minister of Health on the nature and focus of health research within South Africa and co-ordinate such efforts.[14]

Therefore, now that most of the Act is operational a more comprehensive system regulates research by establishing three layers of scientific, ethical and policy controls. However, the National Health Act does not require the three structures (the MCC, NHREC and NHRC) to work together. For example, the Act does not establish a forum where the three bodies could meet and discuss common issues, whereas section 24 of the Act[11] sets up a National Consultative Health Forum between various national and provincial role players which aims at promoting interaction, communication and the sharing of information on national health issues.

In this context it is possible that unclear roles and relationships between institutions may lead to future complications including the regulation of clinical trials of HIV vaccines.

Ethical review of research should be conducted by appropriate ethical review bodies

International and national ethical guidelines provide that research should be reviewed by RECs. Ideally, these should be representative, resourced, capacitated, required by law to use national ethical guidelines and be accountable to other structures.

Prior to the operationalisation of the National Health Act[11] there were no laws in South Africa regarding the functions of RECs and the only statutory safeguard against possible poor performance was for the MCC to refuse to approve research on the grounds that it had not been assessed according to prescribed ethical criteria. Practically, however, it would have been difficult for the MCC to inquire into the work of RECs. Existing guidelines provided some guidance on the composition, functions and performance of RECs. These included *Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa*[15] and *Guidelines on Ethics for Medical Research: General Principles*[16] issued by the Medical Research Council that regulate research undertaken by the MRC or on its behalf.[12] Although not legally binding, these documents set standards for research that a court is likely to use if it were to review REC decisions.

In the past it was difficult to establish the capacity of RECs to review research. Unless RECs voluntarily agreed to an audit there was no way of assessing their composition or procedures. This situation will change now that the National Health Act[11] has been operationalised, as section 73 provides that all RECs should be registered with and audited by the NHREC. This may create a valuable mechanism for regulating the capacity of RECs as the NHREC is able to set norms and standards with which RECs will have to comply when they seek initial and ongoing registration with the NHREC. RECs that do not meet NHREC criteria will be unable to register and retain their status. It is unlikely that the MCC will approve a trial protocol that has been approved by an unregistered REC.

The implication for HIV vaccine trials is that South African RECs with varying appreciation of the ethical-legal complexities may have reviewed protocols.

National ethical guidelines and standards should exist to guide ethical review

Since the publication of the Nuremberg Code[6] in 1947, ethical guidelines have been seen as an essential safeguard for research participants. RECs should be compelled by law to

follow national ethical standards. National ethical guidelines on HIV vaccine research and development are necessary.

In the past only the MRC was required by legislation to ensure that ethical standards were developed to regulate research. However, these ethical guidelines applied only to MRC staff or to research undertaken on the MRC's behalf.[17] The DOH's GCP guidelines[15] are national guidelines but essentially refer to clinical trials only. This means there was no set of national ethical guidelines applying to all health-related research.

Now that the National Health Act has been implemented the NHREC will be empowered to issue national ethical guidelines governing all health research in South Africa. Included in the role of the NHREC, described in section 72(6) of the Act, is the setting of norms and standards for conducting research on humans, including clinical trials. These guidelines have been produced and were launched in April 2005.

There are also guidelines issued by the MRC entitled *Guidelines on Ethics for Medical Research. HIV Preventive Vaccine Research.*[19] These guidelines are an adaptation of the UNAIDS (2000) *Ethical considerations in HIV Preventive Vaccine Research.*[5] They were launched in April 2005 and have been endorsed by the interim NHREC. The MCC's HIV Vaccine Clinical Trials Group is also developing draft HIV/AIDS vaccine trial guidelines that include recommendations regarding the conduct of HIV vaccine trials.[20]

There are two implication of this. Firstly, certain phase I HIV vaccine trials were reviewed and implemented without the guidance of national standards dealing directly with HIV vaccines. Secondly, it is uncertain how consistent the MRC and MCC guidelines will be on substantive issues.

Laws should exist to protect trial participants

Ideally, specific legislation should exist to protect trial participants. This should include provisions relating to the conditions under which research may be conducted on vulnerable groups (e.g. children), informed consent, confidentiality and privacy related to research participation or diagnosis/treatment, compensation for trial-related injuries and protection from HIV-related stigma.

In South Africa legal protection of trial participants is scattered through various pieces of legislation. For example, research participants have the right to participate in research only if they have given informed consent, as set out in the South African Constitution,[21] and participants are protected from some social harms such as unfair discrimination against applicants/employees based on HIV status, as set out in the Employment Equity Act of 1998.[22] This means that obtaining a clear picture on protections for participants is difficult (Barrett Grant C, Strode A – unpublished data, 2001). The National Health Act[11] attempts to deal with this vacuum in s 71 by setting out some of the conditions for research with human subjects. However, this section, which is yet to come into operation, has been heavily criticised for a number of reasons including that it is not comprehensive and is inconsistent with other legislation.[24] Additionally, a number of pieces of legislation that are pending but have not been finalised, have implications for the conduct of trials including HIV vaccines. An example is the Children's Bill[23] that deals with the age of consent to medical treatment and by implication the age at which some legal commentators may regard children as capable of consenting independently to 'therapeutic' research. There is also limited legal protection for vulnerable groups such as commercial sex workers. A number of legal issues have not been fully researched, e.g. the impact of vaccine-induced positivity on international travel and immigration. The implications are that HIV vaccine trials have taken place despite the inconsistent, ambiguous and incomplete nature of the legal framework.

Mechanisms should exist to monitor and enforce legal rights and ethical standards

Mechanisms should exist to monitor and enforce legal rights and ethical obligations that are accessible to trial participants.

Guidelines recommend that RECs should monitor protocol compliance, records, and progress.[19] This focus on the formalistic compliance with protocol requirements may be at the expense of focus on site processes or dynamic interaction with trial participants. Many RECs do not have the capacity to undertake continuing oversight to ensure that an approved protocol is being implemented according to the approval. Moreover, currently legal redress is difficult, and in some circumstances ineffective. For example, a researcher's unethical conduct can be reported to the Health Professions Council of South Africa (HPCSA) but it is argued by non-governmental organisations (NGOs) that the complainant's version is seldom accepted over that of the medical professional.[24] Legal enforcement may also be constrained by cost, low levels of knowledge of legal rights and limited access to legal services.

The implications for HIV vaccine trials are that many complex trial processes (e.g. the quality of risk-reduction counselling and consent processes) might benefit from comprehensive ongoing oversight by independent bodies.

Conclusion and recommendations

Currently, South Africa has a functioning ethical-legal system that has recently been strengthened through the implementation of the National Health Act.[11] The ethical-legal framework has, for the most part, the necessary institutions and some of the guidelines, but does not have many of the laws needed to protect and promote the rights of persons participating in research, including HIV vaccine trials.

Future effort must be directed at enhancing the ability of the South African ethical-legal system to respond to the complexities of clinical research including vaccine trials. We recommend the following: (*i*) advocate for the DOH to develop policies or regulations relating to the implementation of the National Health Act, clarify how each major structure (the MCC, NHREC and NHRC) will work together in terms of HIV vaccine trials, and clarify the role of the MCC in relation to the NHREC on substantive ethical issues; (*ii*) research the challenges facing RECs in the conduct of ethical review of HIV vaccine trial protocols and how this can be enhanced through law, policy and training; (*iii*) review ethical guidelines (NHREC, MRC and MCC) for adequacy of protections and consistency on substantive issues, generally and specific to HIV vaccine trials; (*iv*) advocate for the finalisation of legislation that impacts on potential participants, including the Children's Bill; and (*v*) develop and assess alternative creative measures to monitor ethical standards and legal rights at sites (such as an independent ombudsperson for monitoring consent processes, use of civil society organisations and community advisory boards to assess risk reduction, social harms) and to ensure comprehensive education for prospective participants on their ethical and legal rights.

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