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Ethical considerations in HIV/Aids vaccine trials

The ethical considerations of such trials are the focus of the HIV/Aids Vaccine Ethics Group (Haveg), which is based at the Pietermaritzburg campus of the University of Natal. Ethical issues are central to local and international debates about HIV vaccine trials, according to **Professor Graham Lindegger**.

Ethics, in general, provides a framework to promote the rights and welfare of research volunteers. Central ethical principles promote respect for the dignity of research volunteers as persons and not merely as means to a scientific end. Ethics is also, however, a necessary component of good science, in that ethical procedures can improve the practice of science. For example, volunteers who feel respected and are convinced that their interests are being protected are more likely to volunteer to participate, adhere to intervention requests, return for follow up and answer questions truthfully thereby increasing the validity of the information.

Haveg

Haveg has been set up under the South African Aids Vaccine Initiative to assist with the national process of preparation for vaccine trials in South Africa. The group consists of behavioural and medical scientists and human rights lawyers, who aim to consider ethical aspects of vaccine trials in South Africa.

Haveg's broad goals are:

- To facilitate ethically sound HIV vaccine trials in South Africa
- Based on recognition and understanding of cultural diversity

Haveg's specific goals are:

- To identify and research major ethical issues in HIV vaccine trials
- To facilitate public debate on ethical issues in various sectors: government, NGOs, local communities and the scientific community
- To develop guidelines for sound practice for various groups: researchers, advocacy groups, community advisory boards and ethical review committees
- To develop training processes for various people involved in vaccine trials
- To disseminate findings, publications, reports and best practice guidelines as widely as possible

About 30 HIV vaccine initiatives at various stages of development are in progress internationally and in South Africa a vaccine may be ready for testing in clinical trials within the next two years. The trials will probably run over three to four years before conclusive results become available. Ethical protection for participants in these trials is critical because of unique factors that increase risks to participating individuals and communities. One such factor is that HIV/Aids is a condition associated with sex and activities that are often not legally sanctioned. As a result people affected by HIV/Aids can experience stigma, discrimination and even violence. Furthermore, vulnerability to HIV infection is greater where people are marginalised due to social and economic status. Therefore, attention must be paid to minimising potential harms, as well as maximising benefits to the participants in HIV vaccine research.

One of the core ethical areas in HIV vaccine development and trials is informed consent. This refers to the right of volunteers to decide freely whether or not to participate in research, based on a full understanding of relevant information. It is essentially based on respect for autonomy.

A central ethical task in South African HIV vaccine trials will be to fulfill the spirit of informed consent, which means to promote the rights of people to make decisions that are in their best

interests based on a full understanding of the implications of taking part. In this sense, the essential obligation for researchers is to optimise decision-making for participants.

But there are various notions of informed consent. Some are based on ideas of legal indemnity, some on professional ethics, and some on conceptions of morality. There is a potential danger of over-emphasising a legal and professional view of informed consent that functions to indemnify researchers, and downplaying the moral or ethical obligations to participants. To allow vaccine trials the best chance of succeeding in all respects and protecting the interests of all, we suggest that informed consent has to be driven by an essentially moral perspective, concerned with respecting and enhancing human interests collaterally with scientific interests.

Informed consent is usually seen as involving four components: disclosure of information, full understanding, freedom from coercion and formal consent. Participants must have access to relevant information about the HIV vaccine trial. At the very least, volunteers should be presented with information about:

- The rationale of the trial (that is, the reason for developing a local South African HIV vaccine);
- Technical issues such as the nature of the products;
- Possible side effects;
- Unknown outcomes such as there being no guarantee that the HIV vaccine will offer any protection against HIV infection;
- Methodological issues such as regarding placebo and randomisation;
- The kinds of procedures and tests that participants will undergo during the research;
- The risks of physical, psychological and social harm;
- The benefits of taking part, such as the nature of duration of treatment or care available to them if they become infected during the trial;
- The psychosocial implications of taking part, for example, possible stigma;
- The parameters of confidentiality;
- The right to withdraw at any time, without prejudice.

This component - regarding access to information - is complex and may be compounded in South Africa by low levels of literacy and language barriers. In addition, psychosocial information cannot be neglected in favour of technical and methodological information. Concepts such as what it could mean to discover one's HIV status or what the consequences are of stigmatisation are crucial. It is also vitally important for participants to understand disclosed information. This may be particularly challenging with regard to certain technical concepts as well as personal implications. Researchers also need to consider measurements of understanding.

For consent to be genuine it must be given freely. However, participants for certain phases of HIV vaccine trials are likely to come from vulnerable populations, in the sense that their freedom to make choices may be constrained due to negative prevailing conditions. For example, phase three vaccine trials, which aim to test the efficacy of the vaccine in preventing infection or disease, will draw volunteers from populations at high risk of HIV infection. In South Africa, volunteers at high risk of HIV infection are often historically disadvantaged, resource poor communities with inadequate access to health care. Such communities may have inadequate knowledge of science or ethics, or full understanding of the concept of informed consent.

In such vulnerable communities, it is possible that modest material benefits offered to participants

may act as, or be perceived as, undue inducements to participate. South African researchers must make fine distinctions between legitimate benefits for participation versus inducements that act as pressure to participate.

In South Africa it is possible that HIV vaccine research will take place at a site of service delivery, such as a hospital. In this event, potential participants may perceive that the quality of the care they receive is dependent on their decision to participate. Researchers should make every effort to assure participants that service delivery is independent of research participation. In any research setting, volunteers should be constantly reassured of their right to withdraw without prejudice.

Volunteers must also have the capacity to consent. This raises the issue of whether minors will participate in South African HIV vaccine trials. According to South African law, people below the age of 21 are regarded as minors. Minors should only be involved in research when the requisite legal consent has been obtained and other conditions have been met.

Informed consent is also founded on the notion of individuals as the source of decision making. There has been debate about whether individual, first-person consent is universally appropriate. In cultures or communities where people are defined in terms of their membership to communities, consideration has to be given to whether first person consent should be sought or whether it would be acceptable to get consent from a proxy, such as a husband or traditional leader. It has been generally established that seeking first-person consent is one of the best means of preventing exploitation and should be upheld.

Concern has been expressed that such ethical standards as informed consent in vaccine trials may involve the imposition of a Western cultural frame of reference with a concomitant failure to recognise, respect and incorporate cultural norms. Such concerns about cultural issues may be further informed and influenced by anxieties arising from a disparity in power between researchers and participants on the basis of economics and education.

The need to be sensitive to such local and cultural norms in the preparation and implementation of vaccine trials has been well recognised and is reflected in various guidelines for vaccine trials. There is the possibility that absolute cultural norms may at times obscure oppressive practices, with the risk that vaccine trials could reinforce and perpetuate such practices, if they fail to question them, effectively compromising the ethical principle of first doing no harm. It would seem to us that it is this confrontation of ethos and ethics that is a pivotal aspect of vaccine trials in developing countries like South Africa, and one that will require ongoing debate and consideration on the basis of feedback from trials.

The risks of participation to volunteers taking part in an HIV vaccine trial must be reduced to a minimum and efforts made to actively promote the welfare of participants. Considerations in this regard include physiological risks such as unknown side effects or reactions. A wide range of psychosocial risks may present themselves. These include:

- 'Participation fatigue' that comes with lengthy research;
- The potential for stigmatisation;
- Volunteers may feel 'protected' by the vaccine and this false sense of security may lead them to engage in more high risk behaviour;
- Participants who receive the vaccine may produce antibodies and test positive for antibodies on standard HIV screening tests.

A most contentious issue is whether participants who become infected during the course of a trial should receive treatment. Infection would occur as a result of ongoing risk behaviour in those receiving placebos and also in those receiving the vaccine if it failed to be effective. Positions in this debate have ranged from making available the "best proven therapeutic method" at a level available in industrialised countries or providing the level of treatment readily available locally. There is no consensus in this regard. International guidelines recommend dialogue between sponsors and host country scientists, community representatives, affected populations, non-governmental organisations and government officials to determine the parameters of a care and treatment package. In addition, the guidelines recommend that the "highest attainable level of treatment" is provided.

Attention also needs to be paid to the obligations owed to South African volunteers who test HIV infected during volunteer screening and are excluded from the trial for this reason.

The use of placebo is justified in initial HIV vaccine trials because no alternative prevention intervention is known. Once a relevant vaccine is shown to be moderately effective, future candidates should be compared to it instead of to placebo controls. However, there is some controversy about the level of efficacy to warrant replacing placebo in the control arm of a trial.

The principle of justice demands that those people who bear the burdens of research should have access to the benefits. Trial participants, the community from which they are drawn and high risk groups in the country in which the trials are conducted are identified as priorities for access to any vaccine of demonstrated efficacy. Mechanisms are in place to facilitate such access. In South Africa the first main approach to vaccine development aims to produce a local vaccine that is cheaper than products developed abroad. The intellectual property will be owned within the country.

However, it may take years after a phase three trial for a successful vaccine to be licensed, manufactured in bulk and made available to the community where the research took place. Therefore, other social benefits, such as capacity development, should be negotiated and made available during and after the research to the community from which the volunteers are drawn.

Ethical considerations suggest that every effort should be made to promote the ability of volunteers to make decisions about trial participation that are in their own best interests, regardless of outcome. Recruitment into a clinical trial should be seen as only one possible outcome at the end of a bilateral, but ethically sound, decision-making process involving volunteers and researchers.

Professor Graham Lindegger is the principal investigator at Haveg.