PAPER

Ethics, human rights and HIV vaccine trials in low-income settings

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Received 15 July 2011
Accepted 23 October 2011
Published Online First 6 December 2011

ABSTRACT

The massive growth in global health research in past decades has posed many challenges for its effective ethical oversight, not least of which is how best to provide effective protection of research participants. The extent of the HIV epidemic in sub-Saharan Africa in particular makes research into prevention technologies for HIV, including HIV vaccine research, a global priority. However, the need for vaccine research must be considered in conjunction with the individual's right to informed consent, which is based on the principle of respect for autonomy. One of the primary human rights violations likely to occur in the context of HIV vaccine research is that potential research participants may not fully understand what participation in research studies entails. People who elect to enrol in HIV vaccine trials are required to understand both the potential negative effects of participation (eg, discrimination) as well as complex scientific concepts such as randomisation and prophylaxis in order to be ethically enrolled. In this study, two vignettes are presented to illustrate two core issues in conducting phase III HIV vaccine trials in low-income countries—namely, (1) from the perspective of participants, the extent to which understanding is a prerequisite for consenting to participate in a trial, and (2) from the perspective of trial investigators, whether it is appropriate to persuade eligible people to enrol in a trial, even though their initial reaction is to decline to participate. These vignettes are used to analyse these issues through the prisms of research ethics and human rights in order to identify helpful synergies. It is argued that the human rights perspective provides a helpful lens on ethical issues.

INTRODUCTION

The massive growth in global health research in past decades[1 2] has posed many challenges for its effective ethical oversight, not least of which is how best to provide effective protections of research participants.[3] The debate about adequate protection of participants has been brought into focus by the emergence and re-emergence of epidemics of preventable diseases, such as HIV, TB and malaria, the relentless toll of which on human survival in the poorest countries largely reflects the consequences of increasing global inequalities in power and resources.[4 5] These same inequalities have led to increasing concerns about the risks of exploitation of vulnerable participants from poor communities or countries in research studies. Consequently, the acknowledgement of structural inequalities has spawned a large literature on measures to prevent such exploitation with particular reference to international health research.[6–10] Yet, despite increased attention to strengthening ethical oversight of health research, there has been little attention directed at assessing whether institutional review processes are effective in improving the protection of participants in such studies.[11]

Given that many of the key challenges to conducting ethical research in developing countries have to do with prevention of violations of participants' human rights, it is appropriate to explore the role of a human rights analysis in contributing to ethical oversight. London[12] suggests that rights analyses may be helpful in ethical oversight by contributing to clarifying diverging interests and allowing greater weight to be placed on the rights of participants from vulnerable groups during the review process. Hyder and Dawson[13] argue that, in deciding what a reasonable standard of care should be for clinical trials in a developing country, the benchmark should be a level of care that 'ought to be delivered' under conditions appropriate to a national system of healthcare for that country. Such a standard then starts to speak to normative standards for the right of access to healthcare. For example, the provisions of the Helsinki Declaration about the standard of care that should be provided in clinical trials were subject to wide debate,[14–18] prompted in large part by the use of placebo in the control arms of trials for the prevention of mother-to-child transmission in developing countries.[19] The argument that it was acceptable to provide to controls a standard of care current in a particular country was severely criticised for allowing a double standard between developed and developing countries, and also because of arguments related to providing universal access to education and health,[20] a claim couched in rights language as much as ethical argument. Partly the result of the rights-based arguments, subsequent revisions of the Helsinki declaration have sought to balance opposing views about the use of placebos, most currently represented in the formulation that the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention with very strict exceptions.

A human rights approach may offer a more explicitly defined normative framework for addressing questions of standards than a bioethics approach. Given what is now known about the impact of social inequalities on health it is no longer acceptable to view the question of bioethics

as separate from broader considerations about equity and access.[21] International instruments and documents focus attention far more broadly than on decontextualised notions of consent and participation.[22–24] What is defined as unacceptable practice lies in the realm of human rights violations and is proscribed by adherence to national or international human rights law. However, the question arises whether such a normative framework offers any help in dealing with the difficult questions that arise in ethics review, particularly in developing countries. For example, it is possible that tools that include human rights principles might usefully assist ethics committees in review of research proposals. However, the question arises whether such a normative framework offers any help in dealing with the difficult questions that arise in ethics review, particularly in developing countries, and whether tools to assist ethics committees including human rights principles in review of research proposals might be useful. We examine these questions in the context of HIV prevention research related to vaccine development.

THE CASE OF HIV VACCINE RESEARCH

The issues associated with informed consent are thrown into sharp relief when we consider clinical trial research involving agents that are to be tested primarily or partially for prophylactic rather than for therapeutic purposes. It is well established that there are major financial investments internationally in pharmaceutical and biotechnology research[25 26]; any company that develops an HIV prevention vaccine, for example, stands to make enormous profits. At the same time, the extent of the epidemic in sub-Saharan Africa in particular, makes research into prevention technologies for HIV, including HIV vaccine research, a global priority. Researchers in the field of HIV vaccine research face the challenges associated with administering potentially harmful candidate vaccines to populations that are HIV-negative and not ill. Although the benefits of such research, if successfully implemented, are considerable, the possibilities for abuse and unintended negative consequences are also great.[27] Current HIV vaccine research, furthermore, is undertaken against the real-world background of a recent trial which suggested that vaccine recipients might have been more at risk of contracting HIV than were those who received a placebo.[28] Recent studies outside of the peer-reviewed literature suggest that pre-exposure prophylaxis (PrEP)—Iprex, FEM PrEP, Partners PrEP and TDF 2—has added complexity to the nature of information that must be given to research participants. The field of HIV vaccine research, therefore, is an excellent one in which to explore simultaneous ethical and human rights dilemmas and to identify possible synergies for ethical oversight of biomedical research.

The process of developing and testing a vaccine is complex. In order to test the efficacy of a viable candidate vaccine that has undergone phase I and II testing, large numbers of HIV-negative people at high risk of HIV infection are required to enrol in a large-scale phase III clinical trial. Many barriers to enrolment may make potential participants decline the invitations of investigators to join a clinical trial. Participants will have to contribute their time, respond to intrusive questions about their sexual behaviour and contend with the potentially negative reactions of their family and friends.[29] Previous research suggests that many participants in HIV vaccine trials worry about vaccine-induced seropositivity, physical side effects, including those that may affect reproductive ability, and the likelihood of being subjected to trial-related stigma and discrimination.[30] Persons who elect to enrol in a phase III trial are also required to understand complex scientific issues in order to meet ethical standards for enrolment. These issues include concepts such as prophylaxis as opposed to treatment, the placebo effect, and procedures related to double blinding. It may be difficult for trial investigators to ensure that potential participants with little knowledge of such scientific concepts understand all the scientific aspects of a phase III trial, as well as the potential consequences of their enrolment for themselves.[31]

Two issues come to the fore when considering the conduct of phase III HIV vaccine trials in low- and middle-income countries— namely, (1) from the perspective of participants, the extent to which understanding is a prerequisite for consenting to participate in a trial, and (2) from the perspective of trial investigators, whether it is appropriate to persuade eligible people to enrol in a trial, even though their initial reaction is to decline to participate. We present two vignettes to elucidate these issues and analyse them through the related but distinct prisms of research ethics and human rights in order to identify helpful synergies.

Vignette 1: is understanding a prerequisite for consenting to participate in scientific research?

Dr Gobodo is the principal investigator of a phase III clinical trial in which a promising new HIV vaccine, H-VAC, is to be tested for efficacy. One of Dr Gobodo's main objectives is to recruit at least 2000 HIV negative people who are at high risk of seroconversion to join the trial. She will randomly assign her participants to two groups, one of which will receive the active vaccine while the other will receive a placebo. If there is a significantly lower rate of infection in the H-VAC group than the control group, this will provide evidence that H-VAC is able to prevent HIV infection. Such a result would have positive implications for the public good in sub-Saharan Africa where HIV is most prevalent.

However, Dr Gobodo is experiencing problems in recruiting people to join the trial. Before enrolling, potential participants must agree to undergo certain procedures specified by the trial protocol, such as regular clinic visits, subcutaneous injections and regular HIV tests. In order to provide consent to undergo these procedures, they need to understand a number of different aspects of the trial. These include complex scientific concepts such as randomisation, the role of chance in influencing study outcomes, the role of placebos in the trial, the fact that they may not benefit as individuals from participating as H-VAC has not been shown to be effective, and that adverse events such as physical reactions to H-VAC may occur during the course of the trial. Dr Gobodo must ensure that these concepts are properly explained to, and understood by, all potential participants.

It is in the trial participants' interests to have a high level of understanding of what is expected of them and of possible adverse events that might occur during the course of the trial. Based on a thorough understanding of the possible adverse events that may occur, some potential volunteers may be deterred from participating. Dr Gobodo, on the other hand, wishes to retain as many volunteers as possible, or else she will not have enough participants to run a successful clinical trial. In the process of eliciting informed consent from potential participants, she must consider the following issues:

1. What is the appropriate level of understanding necessary for people who are asked to participate in a clinical trial, that will enable them to make the best decision for themselves about whether or not to enrol? This question addresses the issue of minimal standards that clinical trial researchers such as

Dr Gobodo need to adhere to when recruiting research participants.
2. Have normative standards been met to ensure that participants understand what they are expected to understand?
3. Are the methods that Dr Gobodo uses to assess participants' understanding effective? This question addresses the issue of identifying the most effective and economical method of assessing understanding that may be applied before enrolment of trial participants.

The identification of standards has traditionally been an ethical matter while the assessment of understanding is usually thought of as a problem of psychometrics. Yet, these questions are closely related to each other. They signal a problem that has become highly salient in many developing countries where low levels of literacy and linguistic diversity combine to create conditions under which determining standards for and measuring understanding are complex and multifaceted. From a human rights perspective, many of the antecedents of low literacy are themselves results of absent, failed or inappropriate policies, so that which is taken as a given in an ethical analysis, would be regarded as part of the problem in a human rights frame.

In practice, clinical trial investigators such as Dr Gobodo might be concerned with the minimum requirements expected of them to ensure understanding among trial participants in order to obtain approval from university ethics committees and institutional review boards. Given the absence of objective standards to ensure necessary levels of understanding, various difficulties in measuring understanding, and the likelihood of information decay over time, it might be unlikely that trial participants would at all times be aware of the details of the studies in which they were enrolled.

Vignette 1: using an ethical framework

The ethical conflict reflected in this vignette results from a contemplation of compromised standards of informed consent in order to expedite urgently needed research. Individual good therefore comes into conflict with the common good.

Informed consent in general is based on the principle of respect for autonomy.[32] In research, the concept of informed consent has its origins in the Nuremberg Code[33] and is further elaborated in the original 1964 version of the Declaration of Helsinki and revisions[34] and the Belmont Report[35] where it is discussed as a requirement of the principle of respect for people.

Informed consent is widely accepted as a process rather than an event.[32] As such, there are several components to the concept and several steps in obtaining consent for research. The threshold elements of consent include ability to consent and voluntariness. The information elements include trial-related details that must be provided as well as an understanding of this information. Finally, the decision elements involve a decision to participate or not, and authorisation of this decision if indicated.[32] Clearly, inadequate understanding invalidates the consent process.

Various regulatory frameworks specify the nature of information that must be included in a consent form. In the USA, federal regulations require a minimum of eight items as outlined in the Common Rule (45 CFR 46). These include an understanding that participants are invited to participate in research, risks, benefits, alternatives, voluntariness, confidentiality, research injuries and contact details of site staff.

Some tests of understanding such as the Quality of Informed Consent (QuIC) are based on these eight elements.[36] Other measures of understanding in the field of HIV vaccine research specifically require participants to score a minimum of 80% in order to be enrolled.[37] Given the complexity of HIV vaccine research, the wide range of risks, and the prospect of limited individual benefit, such stringent criteria for understanding may well be justifiable. South African regulatory requirements specify 27 elements that must be included in a consent document.[38] Given these disparate criteria, it is therefore difficult to establish an acceptable minimum standard of understanding.

Measuring understanding is problematic owing to the confounding effect of recall in conducting a test of understanding. As such, the timing of such a test is critical. For the purposes of enrolment, a test administered soon after consent information has been imparted and before enrolment provides an indication of the participants' understanding of the research project at that time. Maintaining such understanding can only be achieved by repetitive discussions of trial-related information as the trial progresses—a much neglected area in the clinical trial process.

It is evident that respect for autonomy establishes the obligation of individual informed consent in the context of research. The principle of respect for autonomy is recognised in the ethical theory of liberal individualism where the participant, as an individual, enjoys a right to all trial-related information that will allow him or her to make a decision. On the other hand, a communitarian perspective may support infringement of individual rights in the interests of public health and benefit to communities.[27] Locating informed consent in a collective context would potentially justify a lower standard of individual consent and hence require a lower level of understanding in the context of HIV vaccine research. The challenge presented by such an approach resides in urban communities in South Africa many of which have embraced the principles of liberal individualism and which will therefore prefer high levels of understanding as part of an individualised consent process.

From an ethical perspective, individual understanding of consent information cannot be negotiated in the interests of science and society. The responsibility for imparting consent information and ensuring understanding by participants therefore rests squarely on the shoulders of investigators and sponsors. For investigators, it means training large numbers of research assistants and site coordinators/research nurses to assist with the detailed consent process that is required. It means that investigators in South Africa will have to be integrally involved in the wording of consent documents so that information is imparted in participant-friendly language. In addition, care must be taken in translating documents into local languages—again ensuring that such translations are not made by language departments using academic language styles. It is advisable that research teams employ translators at sites to assist with the verbal consent process. Additional consent tools such as flip charts, videos and computer programs may need to be developed to augment the presentation of trial-related information. Sponsors similarly need to make budgetary provisions for a comprehensive consent process that will enhance understanding and test understanding at random during the course of a study.

Vignette 1: a human rights commentary

Paramount to a human rights perspective is the preferencing of the interests of vulnerable people and groups in ways that enable them to change the conditions of their vulnerability. There are two ways in which this plays out in this research vignette.

First, it affects researchers in imposing additional obligations because of state failure to honour its human rights obligations:

those participants who are most likely not to comprehend or to have the lowest levels of comprehension are precisely those groups which are disadvantaged and which are marginalised by state action or state inaction. To accept their lack of literacy or poor education is to legitimise what is essentially a rights violation by a state party. Rights are indivisible and interdependent.[39] By denying poor communities adequate education, states also deny such communities their rights to decide whether and how to participate in research (and whether and how they can benefit from scientific research) as well as other rights (dignity, access to information, etc). So, researchers faced with a situation where one group of people has less ability to make decisions as a result of a state's failure to meet its human rights obligations, should be expected to do more than they would have done for a 'normally' educated population.

The standard offered by a human rights approach is normative and outcome-oriented, rather than only process-oriented.[40] A rights-based approach would question whether the information provided enables the person (and the group) to exercise their other rights. In other words, would a participant be provided with sufficient information and insight to enable him/her to act independently and in his/her own interest (or their child's should the child be the participant)? One criterion may be the notion that the participant would be able to explain the study and their reasons for participation/non-participation to a third party. Irrespective of what information is provided, how much, where and when, the expectation would be that the participant would understand the benefits and consequences of participation as well as any other better educated and literate potential participants. Ensuring this level of understanding implies allocating more resources or providing more information to vulnerable participants to ensure that their understanding is equivalent to others who are less vulnerable. It follows then that the test of non-discrimination should be the second criterion of a human rights framework. One would expect all patients, irrespective of educational background or literacy, to have, display and act on an equivalent level of understanding. Settling on anything less, for example, for poor rural illiterate women, would be discriminatory and legitimise antecedent discrimination.

Second, a rights framework that prioritises vulnerable groups does so by imposing obligations on the state to protect them from violations by third parties[40]—in this case, the research enterprise recruiting participants into a study. Thus, it is expected of the state to set standards and put in place mechanisms for ethical oversight. A rights framework does not and cannot provide the details of what type of tests, what level of comprehension and what score a research participant should achieve for demonstrating comprehension, just as it cannot specify the number of houses the government should build or the number of patients who should be on antiretroviral treatment. It can, however, say that a level of understanding that is so low that it violates a participant's dignity and agency is not acceptable.

It is well recognised that in community-based studies, participation rates are generally inversely related to social class, with wealthier communities having lower participation rates and poorer communities generally demonstrating higher participation rates. This is attributed to financial incentives and high rates of unemployment, and what is seen to be a greater degree of altruism in being willing to come forward to advance scientific understanding. Of course, there will always be a background of potential self-interest in expecting unsaid benefits such as a medical examination. Nonetheless, the key question is whether such increased rates of participation are the result of information imbalances and discriminatory standards when seeking participant understanding for entry into studies.

From the point of view of trading off rights in order to achieve a common good, a human rights framework does recognise that there are instances in which limiting a right may be justifiable—either to enable others' rights to be met or to achieve a demonstrable public good. So, it is conceivable within a rights framework to accept that limits to autonomy could be justified under certain circumstances where the public good is overriding. This means that in theory, at least, advancing public health might justify limiting participants' rights to autonomy in the consent process.

However, a rights framework would set requirements for any such claim to be met. First, the decision to limit a right must meet the standards set for being "reasonable and justifiable in an open and democratic society based on human dignity, equality and freedom" (see box 1). The decision to limit a right would require a consideration as to whether the study outcomes would realistically result in the benefits claimed and how important the benefits (of seemingly urgently needed research) might be deemed, whether there were other ways to achieve the purported benefits of the study, which did not necessitate skimping on informed consent, and on the likely severity of the right infringements. Second, the notion of non-derogability of certain rights in times of emergency, gives us a sense of the fundamental importance of maintaining certain rights irrespective of the benefits to be gained from a waiver of such rights. In the South African constitution, rights such as dignity and equality are deemed non-derogable, so any practices that result in limitations of these rights, as might occur through short-cuts in the informed consent process, might be considered so extreme a rights violation as to be unjustifiable, even in the event of large-scale public good. In countries lacking such a constitutional framework, or where research ethics committees are not as well developed, there would be an added obligation on researchers to act on the basis of respect for human rights. A human rights analysis would therefore argue that unless consent is considered in a way that preserves participants' dignity and avoids

Box 1 Limitations of rights: when might they be justifiable?

Criteria set out in the South African Bill of Rights*:
- The nature of the right;
- The importance of the purpose of the limitation;
- The nature and extent of the limitation;
- The relation between the limitation and its purpose;
- Less restrictive means to achieve the purpose.

Conditions contained in the Siracusa Principles†:
- Restriction is provided for and carried out in terms of law;
- Legitimate objective;
- Strictly necessary in a democratic society to achieve objective;
- No less intrusive and restrictive means available to achieve same objective;
- Not arbitrary, unreasonable, discriminator.

*South African Constitution.
†UNECOSOC, 1985.

discrimination, lowering the level of understanding required cannot be justified, no matter how much good can be claimed to arise from the study. Such a position provides a very strong normative standard against which to benchmark justified limitation but does not remove the need for being culturally sensitive, since across cultures, the understanding of what is respect for dignity may differ.

Vignette 2: persuading people to enrol in HIV vaccine trials—or not

Dr Mau is the principal investigator of a phase III clinical trial in which a promising new HIV vaccine, VAC-007, is to be tested for efficacy. The aim of the trial is to determine whether VAC-007 offers protection from HIV infection to those trial participants who receive it. Once a vaccine has been shown to be effective against HIV in a clinical trial, it may be made available to the public and will play an important role in reducing the number of infections in sub-Saharan Africa. One of the sites of the trial is a mining community in Botswana, where the HIV incidence rate is very high. Dr Mau hosts a series of meetings in the community at which he and his colleagues invite the people to hear about the trial as a way of preparing them for the trial initiation. The purpose of the meetings is to provide information so that sufficient HIV negative people from the community enrol in the VAC-007 trial.

Despite information on the trial and the likely benefit to society, it is clear during the meetings that many people are reluctant to enrol. When Dr Mau asks why, they give a wide range of reasons, including, for example, that they fear contracting HIV from the VAC-007 vaccine, that they are worried about health-related side effects, that they are suspicious about Dr Mau's motives as a researcher in their community, that they do not understand what is meant by the term 'randomisation' and the concept of a double-blind placebo, that they would not know how to explain their participation to their sex partners, and that they are worried about stigmatisation and discrimination that may be directed at them because of their involvement in the trial. Dr Mau, on the other hand, needs to recruit as many volunteers as possible for his study. He needs them to enrol and to agree to be randomised to either the candidate vaccine or the placebo condition. He wishes to know how best to persuade these unwilling people to participate without coercion.

Previous studies have shown an association between willingness to participate in HIV vaccine trials and a range of factors, such as perceived personal risk of HIV infection, improved knowledge of HIV and HIV vaccines, attitudes towards HIV and AIDS, and engaging in health-promoting behaviours. On the basis of these findings, Dr Mau devises an educational programme to help miners realistically appraise their level of risk, increase their knowledge about HIV and HIV vaccine trials, and develop a more positive attitude towards trial enrolment rather than HIV. He hopes that by changing these factors, more people will be willing to agree to enrol in his trial.

Dr Mau's research agenda is in keeping with a scientific objective of recruiting a large cohort of willing and available people for his trial. From his perspective, it is in the interest of science for people at high risk of contracting HIV to enrol. However, people who are hesitant to enrol understand that it is possible that no benefits will accrue to them and, indeed, they may have adverse effects. The tension between these competing perspectives creates a quandary for researchers interested in the social good of a well-conducted and appropriately powered HIV vaccine trial, on the one hand, and ensuring autonomy and freedom from psychological and social manipulation of potential trial participants, on the other.

Vignette 2: using an ethical framework

Provision of informed consent in research occurs strictly on a voluntary basis.[32] This means that consent must be free of coercion or undue persuasion. The notion of voluntary informed consent has its origins in the Nuremberg Code of 1947. This document was developed in the aftermath of World War II in the context of non-voluntary research conducted on vulnerable prisoners in the concentration camps in Nazi Germany.

When participants are vulnerable and an asymmetrical power relationship exists between researcher and participant,[27] voluntariness of consent becomes precarious and fragile. Under such circumstances, greater levels of protection of study participants must be afforded as it is evident that vulnerable participants are more susceptible to 'persuasion' than are non-vulnerable participants. Surveys have shown that willingness to participate in HIV vaccine research is inversely related to educational levels.[41] Persuading research participants may reflect a malalignment of the interests of researchers and participants. Though some would argue that the concepts of persuasion (which is viewed as acceptable) and coercion (which is viewed as unacceptable) are ethically distinct, in practice, and especially where power relations are heavily skewed, it is not always easy to distinguish between the two. As Powers[42] [p140] notes, "Ethicists charged with determining whether an action is ethical or unethical should be wary of relying only on legal and scientific definitions of persuasion and coercion". In HIV vaccine trials, the blurring of persuasion into coercion because of the power issues at stake is a particular concern. While the goals of scientific research are laudable, aiming at benefit to medical progress and benefit to all of humanity, in many research settings, at an individual level, researchers usually have more to gain financially and academically, than participants.

Virtue ethics theory[32] has traditionally been applied to clinical medicine and attempts to provide a response to the question: "What does it mean to be a good doctor?" Extrapolating virtue ethics to the research setting would require a virtuous scientific investigator to be compassionate, honest, trustworthy and to posses integrity. Such virtues place an obligation on researchers to communicate trial-related information to participants in a transparent, honest, factual manner. Scientific integrity obliges researchers to respect the decision of participants to decline participation in research.

Recognising the biased position that individual researchers may find themselves in during the conduct of a clinical trial, the Declaration of Helsinki[34] advises that an independent person be responsible for the consent process in situations where consent may occur under duress or in the setting of a dependent relationship. Such a person would be responsible for dissemination of trial-related information to participants in an objective manner. He or she would then either obtain their consent to participate or accept without sanction their decision to decline enrolment. Ideally, such a set of circumstances would be regarded as the ethically correct way to obtain consent for research participation. However, in clinical trials, especially in developing countries, resource constraints may not allow the luxury of an independent 'consent doctor' for clinical trials.

Dr Mau—detecting reluctance to participate—would have to explore the reasons for reluctance. Based on these reasons he would need to provide information where lack of information exists, clarify misunderstandings, dispel fears based on facts and allow participants time to reconsider their decisions to

participate or not. He is obliged then to accept their decision. Deliberate 'persuasion' is ethically unacceptable.

Vignette 2: a human rights commentary

A human rights framework is not anti-science. The right of all people to 'enjoy the benefits of scientific progress and its applications' is one of the provisions of the International Covenant on Economic, Social and Cultural Rights (ICESCR; para 15(b)). Researchers such as Dr Mau are not simply conducting a study, but are contributing to the broader goals which are part of a rights framework. This is not to say that Dr Mau will be immune from conflicts of interest or a dual loyalty,[43] but all things being equal, he could be an agent for the realisation of rights—of the study participants, and also primarily for broader society. Of course, it is a long string leading from the study to future benefits, including the possibility of increased access to healthcare, and there are many contingencies on the way, so one cannot claim more than what is evident. Yet, the benefits of scientific research are rights as much as shelter and food. Here, parties who participate in the study are not the parties who stand to benefit the most, if at all. Indeed, we may be in a situation in which participants are asked to 'sacrifice' their own comforts for a broader good. Conducting research into how best to help miners realistically appraise their level of risk need not violate miners' rights if it respects their dignity and agency—that is, their ability to make independent decisions.

It is not as if there is a right to remain 'ignorant' in the same way that there is a right to remain silent when charged with an offence. So, for example, providing an education programme to miners cannot be a violation of their rights, if they are free to decide whether to participate or not, in line with normal ethical standards. Of course, Dr Mau may experience subtle or not-so-subtle inclinations to emphasise certain information which will improve participation, but as long as consent is fully informed, there should be no problem.

An unanticipated (or anticipated) benefit might be miners becoming more active participants in other forms of citizenship if the education is truly able to empower them as a vulnerable group. It may not necessarily mean that their 'active citizenship' will translate into increased participation rates, and that is the chance that Dr Mau must take.

DISCUSSION

A human rights perspective necessarily prioritises the interests of vulnerable people and groups over those of other stakeholders such as vaccine trial investigators, funders, and community advisory boards. HIV is more prevalent among poor, marginalised and oppressed communities, and it is therefore the case that those more vulnerable to HIV face a wide range of other challenges and vulnerabilities. These challenges include limited access to good quality education and information. Not only is HIV risk high in vulnerable communities but these are also the communities in which there are probably the greatest challenges to ensuring adequate comprehension regarding the risks, benefits, alternatives, voluntariness, and confidentiality associated with vaccine trial participation. For good scientific reasons it is important to conduct HIV vaccine research in these marginal communities but paradoxically these communities are also those which are most open to being exploited by researchers.

The challenges associated with ensuring adequate informed consent among people recruited into vaccine trials, even in populations considered non-vulnerable, are considerable. Highly educated people with tertiary qualifications who are unschooled in the language of science, may have difficulty in understanding complex concepts such as randomisation, prophylaxis and incidence, even when these are explained in everyday terms. If it is a challenge to inform these populations adequately about trial participation, this challenge will be even more acute with more vulnerable groups.

There are difficulties in ensuring that all participants in trials have an equivalent level of understanding. A key assumption in determining equivalency of understanding is that such a concept should be measurable and therefore operationalised. The most common approach to measuring understanding is through the use of scales. Such methods will allow trial investigators to compare levels of understanding among individuals who are

Table 1 Summary: ethical and human rights issues emerging from analyses of the vignettes

Ethical issues	Human rights issues
Vignette 1: understanding	
Attention to the criteria and elements for informed consent: guidelines; complicated by difficulties of measuring understanding	Non-discriminatory: what standard would you expect from non-poor and non-vulnerable?
Regulatory frameworks specify the nature of requirements to be met	State obligation to ensure third parties protect people from violation of their rights—hence ethical oversight
Individualism versus communitarianism in the ethical decision-making process draws on need to recognise different cultural contexts	Siracusa principles and Bill of Rights sets out conditions justifying a limitation of individual rights in the interest of common good—strong normative framework, although recognises cultural specificity
Ethical obligation to invest more in training, explanation, counselling to avoid exploitation IN the research process	Exploitation and vulnerability arising BEFORE the research process imposes a rights obligation to invest more in training, explanation, counselling because of vulnerability
	Substantive equality—greater focus on the outcome rather than process—understanding and participation must be non-discriminatory
Informed consent as a process which recognises ability to consent and voluntariness as the two key elements	The attention to process is more about agency of the participants to change their vulnerability (empowerment) than about the checklist comprising informed consent
Vignette 2: 'persuasion'	
Asking participants to carry burden for future benefits of others	Right to benefit from scientific progress could motivate participation or provide complement to purported public health benefits
Informed consent as free of coercion: raises questions about power imbalances between researchers and participants	Education alone is not a violation as long as participants enjoy real freedom to make informed decisions
Highlights role of virtue ethics on the part of the researcher	Participants' willingness to contribute through science to the benefit of the collective
Checks and balances to reduce power imbalances—person external to the study to take responsibility for informed consent	The way education is done should enhance agency of the participants to change their vulnerability (empowerment) rather than reinforce power imbalances
Increasing information to participants may paradoxically reduce participation = conflict of interest	Increasing information to participants may empower participants, which of itself is a positive outcome and which may not lead to lower participation

recruited to participate in prospective trials, and among demographic groups who are at varying levels of risk of HIV infection. Examples of such groups include, for example, people residing in informal settlements, rural farm workers, mineworkers, men who have sex with men and adolescents. However, it has been shown that the validity of such measurement scales is not necessarily optimal,[44] and while it may be ideal to expect different groups to have an equivalent optimal level of understanding, this may not be attainable in practice. Yet, from a human rights perspective, a tolerance for varying levels of understanding, particularly between different demographic groups, may be discriminatory and therefore a violation of the rights of trial participants.

From a human rights viewpoint, the state has a specific obligation to involve itself with, and act in the interests of, marginalised and vulnerable groups. Such an obligation stands in contrast to an ethical framework where the interaction is based on the individual volition of the participant to engage with the researcher, with oversight provided by ethical review committees. Review committees typically concern themselves with issues at an individual level such as informed consent, rather than invoking the state to step in to fulfil its obligations to marginalised and vulnerable people. While it may be argued that a bioethics framework concerns itself with both individual and collective aspects of research monitoring, most research ethics committees concentrate on individual matters such as ensuring informed consent.

There are several disincentives associated with vaccine trial participation. These include the inconvenience of frequent HIV testing, trypanophobia (fear of needles), the possibility of testing HIV positive and stigma and discrimination associated with participation. Given these disincentives, the tendency may exist for trial investigators to engage in programmatic efforts to convince eligible but as yet undecided people to overlook such concerns in favour of trial participation. The question that straddles both a human rights and an ethical framework is that of determining at which point such efforts, officially aimed at exploring and processing issues of decision-making with undecided people, become implicitly coercive. Thus, a continuum exists between exploring with potential trial participants reasons for their reluctance to enrol in a trial, on the one hand, and persuading them to participate in such a trial, despite their reservations, on the other. There are considerable difficulties in distinguishing between the two, yet such a distinction is critical from both a human rights and an ethical perspective.

In conclusion, this article has discussed the challenges around participation in HIV vaccine research in low-income settings such as sub-Saharan Africa, where HIV has reached epidemic proportions. Two core issues have been put forward: (1) from the perspective of participants, the extent to which understanding is a prerequisite for consenting to participate in the trial, and (2) from the perspective of trial investigators, whether it is appropriate to persuade eligible people to enrol in a trial, even when their initial reaction is to decline to participate. These dilemmas have been considered from research ethics and human rights perspectives, which provide interesting and complementary points of view, contributing to a more comprehensive understanding of the complexities associated with conducting HIV vaccine research (please refer to table 1 for a summary of key points). Research ethics committees need to take due regard of the issues of power at stake.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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