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Theoretical Model of Critical issues in Informed Consent in HIV Vaccine Trials

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Abstract

The informed consent (IC) process for HIV vaccine trials poses unique challenges and would benefit from improvements to its historically-based structure and format. Here, we propose a theoretical framework that provides a basis for systematically evaluating and addressing these challenges. The proposed framework follows a linear pathway, starting with the precondition of voluntariness, three main variables of valid decision-making (competency, provision of information and understanding) and then the consequential outcome of either refusal or consent to participate. The existing literature reveals that culturally appropriate provision of information and resultant understanding by the vaccine trial participant are among the most significant factors influencing the authenticity of valid decision-making, though they may be overridden by other considerations, such as individual altruism, mistrust and HIV-related stigma. Community collaborations to foster bidirectional transmission of information and more culturally tailored consenting materials therefore represent a key opportunity to enhance the informed consent process. By providing a visual synopsis of the issues most critical to IC effectiveness in a

categorical and relational manner, the framework provided here presents HIV vaccine researchers a tool by which the informed consent process can be more systematically evaluated and consequently improved.

Keywords

HIV Vaccine Trials; Informed Consent; Theoretical Models; HIV vaccine; HIV

Introduction

The informed consent process (ICP) creates the legal and formal record of a person's willingness to participate in a clinical trial^{1,2}, and as such is integral to all clinical research trials³. Rooted in principles of beneficence, justice and respect for persons⁴⁻⁶, the ICP seeks to obtain true consent, which the Council for International Organizations of Medical Sciences (IOMS) defines as "consent given by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subject to coercion, undue influence or inducement, or intimidation⁷."

The structure and basic format of the ICP has changed little over time⁴ and has been slow to adapt to changes in research, emerging health concerns, community attitudes and societal values^{4,8}. Because of the powerful effect of such changes on HIV vaccine research, UNAIDS has created guidelines to govern the ICP in HIV vaccine trials^{9,10}, which reflect the special challenges^{1,3,9,11-13} associated with such research – including both the sensitive social issues¹⁴⁻¹⁷ and complex scientific concepts^{1,9,14,18} that must be conveyed to trial participants. In addition, HIV vaccine trials face other ethical dilemmas, such as the extent of treatment offered to people who become HIV infected during course of a study¹⁹⁻²⁴. These challenges have been well documented in review studies^{3,9,25}, but there is presently no formal conceptual framework that comprehensively incorporate these issues. Such a framework could have considerable value in defining the components of a system, and thereby revealing opportunities for overall optimization and tailoring to the needs of specific study populations.

Subjective Model of Informed Consent by Meisel et al.²⁶

Meisel et al.²⁶ propose a theoretical psychological model of ICP based on the elements of valid decision-making for clinical trials. The authors describe four main variables that comprise valid decision-making: provision of information, competency, understanding, and voluntariness. The latter is a precondition for the first three, which together form the basis for the *consequential outcome* (consent or refusal).

Voluntariness means that the person making the decision must be free from coercion, unjust persuasions and enticements. *Provision of information* requires that the participant must be informed on the risks, benefits of participation, potential side effects and alternative treatments if applicable. *Competency* refers to the person's capacity to make a valid decision (i.e., is the person capable and reasonably able to make the decision and free from decision-

impairing influences such as cognitive disability). *Understanding* speaks to whether a person comprehends the information that is provided to the extent of knowing the ramifications of their participation. The *consequential outcome* should follow the steps prior to it and is the patient making a well-reasoned and informed choice to consent to receive the study intervention - or refusal.

The proposed framework does not intend to change the traditional concept of informed consent (IC), but rather seeks to visually depict the process components of IC and related challenges in HIV vaccine trials, and provide a needed structure for strategic evaluation (Figure 1). Major advantages of the framework are that its components are both comprehensive and easy to extrapolate to the IC in any clinical trial, including preventive HIV vaccine trials.

Applying the Theoretical Model of Informed Consent Process to IC in HIV Vaccine Trials Pre-Existing Condition

Voluntariness—HIV disproportionately affects marginalized groups (e.g. societal minorities, impoverished communities, and those with chemical dependency problems)^{16,27-35}. Thus, both Phase I/II safety trials and Phase III efficacy trials of experimental HIV vaccines should ideally be tested in these populations. However, vaccine research involving these vulnerable groups comes with an ethical responsibility to guard against unintended coercion of subjects due to poverty, low educational attainment and/or social status and reduced cognitive capacity^{3,36}. In this light, it is important to note that financial compensation for trial participation is viewed by some trial participants as part of the “informal economy” in marginalized communities^{16,37,38}, and even modest financial incentives may have strong effects on behavior, as related to HIV/AIDS¹⁶. Non-financial incentives to participation in HIV vaccine trials may also be significant – and can include improved medical ‘care’ to enrolled volunteers that might otherwise be inaccessible^{16,18,39}.

Monetary incentives can increase willingness to participate in vaccine trials^{17,18,38,40}, yet the nature and amount of incentives remains controversial³⁸. Three main models have been proposed: the ‘wage payment model’, the ‘reimbursement model’ and the ‘market model’¹¹. Unfortunately, none is ideal - and choosing the most appropriate for the specific vaccine trial context is critical. This has traditionally been overseen by the Institutional Review Board (IRB) for each individual study, but remains fundamentally a subjective exercise with little in the way of data-driven policy guidelines designed to minimize coercion while maintaining fairness.

Social desirability also affects the authenticity of voluntariness in vaccine trials^{9,41}. Potential participants may feel the need to please others who are perceived to have power (e.g., medical personnel) in order to make a favorable impression^{9,42,43}. This is especially likely for socially vulnerable groups who may be traditionally disempowered. “Fear of reprisal” is also a concern in this regard, as the intended community may feel that not participating or withdrawal may have adverse ramifications from those in authority. Use of community-based participatory research (CBPR) methods, such as the use of community advisory boards (CABs) or other social advocacy groups⁹ and participation of members of the

intended population in research activities, may help in closing the cultural gap between scientists and the community.

Components of Valid Decision Making

Competency—It is generally assumed that individuals who meet inclusion criteria and are free from mental disorders or the immediate influence of substance abuse, are able to make valid decisions⁴⁴. In making this assumption, researchers may overlook the importance of formally assessing reasoning competencies, and the ability to comprehend study-related information⁴⁴. The existence of multiple reports of insufficient volunteer understanding in the HIV vaccine literature underscores this concern^{9,12} and suggests that more formal assessment of decisional competency should be considered in the inclusion/exclusion criteria for HIV vaccine studies, especially in vulnerable populations⁴⁵. Indeed, it may be possible to take advantage of materials developed in other types of studies (substance abuse, cancer, Alzheimer's disease⁴⁶) or, the short validated decisional assessment instrument developed by Jeste *et al.*⁴⁷.

The cultural competency of HIV researchers is also a critical issue^{48,49} and highlights the importance of cultural responsiveness training of trial staff. Participants stand to benefit if 'cultural reconnaissance' is conducted during the early stages of trial design (i.e. an investigative and immersive effort to understand the cultural and social context of the trial)^{11,48-50} so that research practices are more in keeping with their socio-cultural norms. Consistent with this, many research groups have highlighted the value of community level involvement through the requirement of CAB review of protocols in development,^{11,23,28,48,51-53} however there remains a need to find a way to guarantee effective community input on a consistent basis.

Provision of Information—HIV vaccine researchers are ethically and legally bound to make volunteers aware of all known individual risks and benefits of study participation, as well as the procedures and the underlying scientific rationale for the study. There is however the issue of unforeseeable risks (a concern for participants and researchers alike) — and whether true consent can be achieved in the absence of knowing such information. However, in keeping with the traditional concept of IC, researchers are ethically required to advise participants of the possibility of unknown immediate and/or long-term risks. Participant understanding of the 'unknowns' as an inherent part of clinical trials is crucial, as they must agree to a certain level of potential uncertain risk. However, mechanisms (e.g., external data safety monitoring boards) are in place to continuously monitor and assess all potential risks in order to help ensure the safety of trial participants.

Additional supporting trial information can be provided to participants, however this information and the mode by which it is presented is often left to the discretion of researchers and IRB's. This can lead to misunderstandings, a failure to appreciate the real world perspective of the target population, researcher-biased information and reduced overall participation⁹. For example, researchers may not feel obliged to dispel cultural myths that propagate their own end or inform participants of indirect harm that can occur as a result of their participation, as this may discourage enrollment. Most research groups

attempt to address this concern by instituting permanent CABs, which function to advise trial staff on community perspectives and needs^{11,40,48,49,54}. CABs in conjunction with regulatory ethics boards may also assist by conducting formal *a priori* putative assessments to ensure that information being dispensed is comprehensive, accurate, free from researcher biases, community-specific, and culturally relevant and appropriate, if true IC is to be obtained in keeping with ethical mandates. . This can significantly improve the quality and relevance of recruitment materials and the ICP – as exemplified by the Carraguard Phase 3 microbicide trial (HPTN 035)¹¹, in which the materials used directly reflected community involvement.

A closely related issue is the vehicle by which trial information is communicated to the community. This is strongly influenced by ethos of a given population group⁹. Should someone from the community (e.g., an elder or respected leader of the same ethnic or cultural background) present the information to be in keeping with socially accepted norms?^{9,48,49} To what extent should the representative community member be allowed to speak for the ‘individual’? In what forum should this information be presented (e.g., a community gathering, or the person’s home)? Such questions require further exploration and consideration, especially when researchers from one country (e.g., the U.S.) conduct clinical trials in another nation or region where norms and cultural sensibilities may differ (e.g., South Africa)^{9,10,27,55}. CABs become particularly essential in these cases to ensure that cultural appropriateness is optimally achieved.

It is also important to consider the most effective way to present trial-related information. HIV vaccine researchers have explored media ranging from video⁵⁵, to audiotapes¹³, to physical props, to traditional pen and paper approaches. For many vaccine sites, traditional written documents are the medium of choice - but there is a tension with respect to providing sufficient information without overwhelming participants⁹. Some sites have used a combination of media, with some measure of success^{13,56} - though Flory and Emmanuel’s systematic review of 42 studies on IC processes revealed that no one method is fool-proof²⁵. Again, CABs and/or community partners play a critical role in informing researchers on best modality of information presentation and what works best for their community peers’ reception.

Understanding—HIV vaccine trials must communicate complex information to participants, including concepts such as vaccine-induced seropositivity^{9,18,40}, which are commonly misunderstood by most trial volunteers^{15,40} and/or people they come into contact with (medical provider, family, etc). In addition, other topics such as the meaning and need for a placebo group, the actual vs. perceived protective effect of HIV vaccination, and composition of the candidate vaccine are also unclear for many participants^{13,18,40,55}. Scientists have responded to the complexity of these topics by using instructional and educational videos^{55,57}, developing culturally sensitive consent processes^{11,49}, simplifying the consent form through the use of pictures and lower grade language level^{14,58}, combining audiovisual forums⁵⁶, and using audio tapes¹³ for participants with lower or negligible literacy⁵⁹. Despite this, however, there is a general consensus that more effective methods to deliver these complex concepts are needed, and that they should be tailored to participants ‘learning style’ (visual vs. auditory learner for example) and/or cultural persuasions. The

preliminary evidence supporting person-to-person extended discussion and test/feedback approaches were described as the more effective methods for improving volunteer understanding in the ICP. Care must be taken however, in the interpretation of the observed improvement in understanding results as rote memorization in understanding assessments may have played a role²⁵.

How volunteer understanding is assessed and the validity of assessment tools are thus central concerns in HIV vaccine trials^{3,9,12}. Current assessments of understanding may only measure rote memorization of information, rather than real understanding¹². To address this, a variety of assessments have been developed to better assess understanding - including open-ended questions, more conceptual multiple choice questions, and verbal summation of study material to study nurses^{12,60-62} - though there is still a concern that a significant number of participants are consenting without fully understanding^{6,62}. This also highlights the issue of whether ethical boards should mandate that researchers dedicate resources to more rigorous assessment protocols or leave it to the judgment of principal investigators that may prioritize budgetary constraints over ethical dilemmas such as thoroughly assessing participant understanding.

There is also a need to define, from an evidence-based standpoint, the appropriate level of understanding that is sufficient for trial enrollment³⁷. In practice, this is achieved by researchers selecting an essentially arbitrary threshold score on an evaluation instrument to which participants must meet to enroll- e.g., a “grade” of 81%⁵⁵ or 75%⁶³. This approach however, does not consider whether a participant may have failed to understand a small subset of essential concepts. This issue is compounded by the heavily stigmatized nature of HIV^{17,31,64-66}, which can strongly affect understanding⁶⁷. It is essential that researchers work in concert with the intended community through CABs and other community partners, to raise awareness and communicate accurate information prior to study recruitment^{10,15,28,48,68}.

Consequence

Refusal and Consent—The choice to refuse or consent to participate in a trial is not often predicated on motivational factors such as altruism and perceived positive incentives to participate^{17,40,69} rather than the information provided. In such cases, participants may have decided to or refuse to participate even before the consenting process, the latter decision possibly being rooted in underlying mistrust, stigma or negative stereotypes^{32,33,40}. This is understandable in light of widespread popular awareness of current and past research abuses, notoriously, the Tuskegee Syphilis Study and Guatemala Syphilis study⁷⁰, and requires that HIV vaccine researchers must rebuild trust during trial procedures such as the ICP^{33,40}. For example, it is well documented that African Americans and Latinos have lower participation rates in HIV vaccine trials^{16,30} and that investigators must initiate creative approaches to encourage their participation³⁰. Research abuses and issues of mistrust have been documented in many other countries, presenting a formidable barrier to participation in vaccine trials internationally⁶⁵.

Finally, there is the matter of individual consent vs. community consent^{37,50}. In the United States individual right to choose is highly prioritized and is culturally the norm, however in

more communally minded societies decisions are often made in concert with others – including elders, spiritual leaders, family members and community members⁹. When a person from such a society gives individual consent, it can be important to determine if this decision is reflective of a community approved choice - since failure to obtain “community consent” may have adverse ramifications for the individual⁴⁹ and could even lead to termination of enrollment in that particular community¹¹. However it is also important to consider whether a person’s choice is indeed an individual decision rather than one coerced by group influences. Studies have shown that fear about breach of confidentiality is a strong disincentive for participation^{54,71}. To circumvent these social pressures, measures of confidentiality should be rigidly upheld and individuals reassured that the parameters of their involvement are kept confidential.

Limitations of the Framework

The linear fashion of the framework can limit the application IC as a dynamic process. In its linearity it can suggest that IC goes from point A (voluntariness) to B (decision making) and then end. However, the process of consent can be an ongoing enterprise whereby scientists continually reassess whether a person feels that their decision is voluntary as the trial proceeds, whether they understand the ramifications of their participation and whether more information needs to be provided even after an initial decision is made, to ensure that the person is fully aware, dictating the need for secondary consent. While this may be a limitation of the model, this structure of consent can be applied at various time points along the course of a trial, thus circumventing the apparent finiteness of the proposed model. The model seeks to highlight the primary challenges in HIV vaccine IC but does not include other relevant challenges such as: the evolution of cultural norms towards researcher biases and potential negative consequences of this; how best to assure the competency of investigators in providing accurate information and conducting IC protocols; and to what extent research groups should be held responsible for potential negative consequences of trial participation. Finally, the model still adheres to the traditional concept of consent and may reinforce current ideologies about consent. However, the model is so structured to better capture the current challenges of IC in vaccine trials, which have been bred in the traditional understanding of consent. Changing the fundamental concept structure of consent requires more extensive investigation and the development of evidence-based solutions.

Conclusion

This paper describes a conceptual framework that can be used by HIV vaccine researchers to systematically evaluate and improve IC protocols. Existing consent protocols can be mapped onto the different components of the framework and examined using this perspective, to determine if they are effectively addressing key challenges with respect to the study protocol, target population(s) and individual study participants. By facilitating strategic evaluation, the model challenges researchers to find innovative ways to overcome these existing hurdles, and reform or add to the fundamental structure of consent, to better protect the ethical rights of participants. The model provides a critical synopsis of challenges for participants to consider when engaging in a trial so as to help safeguard their ethical rights. This proposed framework also highlights the importance of carefully considering cultural

issues, and working in close collaboration with the community, in order to develop processes that can be tailored to a wide range of research populations/ settings. Ultimately, this framework provides the foundation for the improvement of the ICP for scientifically complex clinical research in vulnerable populations.

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Figure 1. Theoretical Model of the Informed Consent Process in HIV Vaccine Trials

This model delineates the critical issues in Informed Consent in HIV vaccine trials and organizes them into relational components within a theoretical framework.