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Charles F. Turner and Amy R. Sheon

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Behavioral Studies Relevant to Vaccine Trial Preparation: An Introduction*

CHARLES F. TURNER[1] and AMY R. SHEON[2]

ABSTRACT

Preparations for large-scale trials to test the efficacy of candidate HIV vaccines can benefit in several crucial ways from a targeted program of behavioral and social research. Randomized field experiments testing alternative procedures for the recruitment and retention of subjects can help identify research procedures that will ensure adequate sample sizes while minimizing sample attrition over time. Similarly, assuring that subjects accurately comprehend the potential risks of participation will require more than simply presenting scientifically accurate information. Ensuring both the adequacy and appropriateness of risk communications as well as the accuracy of subject perception of risks (across the social and cultural milieux in which vaccine trials will be undertaken) is a critical task. Ethnographic and behavioral studies can help to ensure that our obligation to obtain truly informed consent from our research subjects is fully met and documented. Monitoring risk behaviors over the course of the vaccine trials could also benefit from strategic investments in new technologies developed by social researchers to permit the collection of sensitive personal data while affording complete privacy to subjects. These new measurement technologies include procedures that permit private data collection (without a human interviewer) in any spoken language and without requiring that subjects be literate.

INTRODUCTION

WE HAVE ALL BECOME ACCUSTOMED (perhaps unwillingly) to agreeing that the behavioral and social sciences have an important role to play in efforts to combat the spread of HIV. As early as 1986, this position had been well articulated by a range of eminent scientific groups and individual scientists.[1–4] The range of roles for the behavioral and social sciences includes developing better information on the patterns of sexual and drug use behaviors in the population, developing more effective interventions, conducting rigorous evaluations of the effectiveness of AIDS prevention activities, and coping with the social consequences of the spread of morbidity and mortality due to HIV infection and AIDS.

It is not merely an automatic reflex to assert that there are parallel and equally important roles for the behavioral and social sciences in the planning, conduct, and analysis of trials of HIV vaccines. Indeed, there is reason to believe that some of the most crucial aspects of testing an HIV vaccine must inevitably draw on paradigms and data from the behavioral and social sciences. Three areas that will require particular attention are as follows:

- Recruitment and retention of subjects
- Adequate communication of the difficult notion of the "po-

[1]Program in Health and Behavior Measurement, Research Triangle Institute, 6101 Executive Blvd., Rockville, Maryland 20852.
[2]Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Solar Bldg., 6003 Executive Blvd., Bethesda, Maryland 20892.

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tential risks" of any particular vaccine (the difficulty of this challenge is compounded by the need to communicate adequately the uncertainty that surrounds our knowledge of these risks)
- Assessment of the extent to which individual subjects are risking exposure to HIV (which is necessary to assess the extent to which vaccines have been challenged)

RECRUITMENT AND INFORMED CONSENT

There has been much concern given in preliminary thinking about conducting HIV vaccine trials to issues of subject recruitment and retention. (See, e.g., the report given at the 1992 conference by the National Cooperative Vaccine Development Group (NCVDG) Working Group on Design and Implementation of HIV Vaccine Efficacy Trials[5]). While general observations have been offered about the importance of "user-friendly clinics," "well-trained, culturally sensitive field staff," and clinic hours and procedures that accommodate subject schedules,[5] it is not clear what the *relative* importance of such factors are to the likely success of subject recruitment and retention efforts. Furthermore, there is even less clarity about what would constitute optimal conditions for subject recruitment and retention.

What is required to answer such questions is, we believe, a program of pilot studies that would gather empirical data to define the relative importance of the various factors that might make subject recruitment and retention efforts more or less successful. Such a pilot effort would not seek merely to demonstrate that one particular strategy for recruitment could yield a particular number of subjects. Rather, the relative effectiveness of different strategies—varying, for example, by the types of personnel, training, clinics, and auspices of the research—would be systematically compared. Conducted as a randomized field experiment,[6] such pilot efforts would aim to provide reliable data on the relative impact of the various components of a recruitment effort.

Obviously, some aspects of the vaccine trials cannot be simulated in pilot studies. Specific data about the safety and efficacy of candidate vaccines and the antibody responses they generate, for example, are unlikely to be known at the time of the pilot studies, and it is likely, in any event, that pilot studies would only simulate the operations of a vaccine trial. There will thus be some inexactness in the translation of the results of these pilot studies to the conditions that would prevail in the actual trials. Even with such imperfections, these pilot studies could provide a noteworthy improvement in our understanding of the relative merits of alternative ways of designing our subject recruitment and retention efforts. The empirical data provided by such pilot studies would be helpful in guiding decision making when large-scale trials are ready to be launched, and we must grapple with the practical problems of identifying, motivating, and facilitating the enrollment and continued participation of subjects in the trials.

Systematic field experiments that pilot test alternative designs for such trials are one of many research methodologies that can provide reliable, empirical data on the likely effectiveness of particular designs in obtaining and retaining subjects in future vaccine studies. We believe that the methodology, tools, and findings of the behavioral and social sciences can also assist us in understanding the societal and individual barriers to recruitment, the crafting of suitable messages, and, if appropriate, the monitoring of compliance.

Informed consent

There is a second, complementary role for behavioral and social science research that is at least as important as facilitating subject recruitment and retention. That role is to assure that the key requirement of truly informed consent is met for any trial that is launched. To the extent that there is to be "social marketing"[7] of the vaccine trials for the purposes of subject recruitment, there should be complementary attention to assuring that

- Potential risks and benefits of the trials are well and fairly communicated to all potential subjects
- Evidence is gathered to assure that these messages do, in fact, communicate those risks to all potential subjects
- Inevitable uncertainties about the reliability of this information are also well communicated

Assuring the adequacy of the risk communications that are central to obtaining informed consent is a daunting task[8] given both the uncertainties that may surround our knowledge of potential risks to subjects compounded by the need to craft, test, and evaluate risk communications appropriate for the multiple social and cultural milieux in which trials will be undertaken. Our ability to carry out these tasks is compromised by the substantial gaps that exist in our understanding of key aspects of risk perceptions—even for the Western populations in which most research has been done.[9–12] In a review of risk perception and risk communication in science and technology, the National Academy of Sciences[8] noted the need to develop a better understanding of

- How people think about the risk decisions that confront them
- How people think about the causal processes that create risks
- How people perceive the social and governmental processes involved in managing (or creating) risks
- How to present complex information on risks both clearly and accurately

Such gaps in our understanding inevitably raise concerns about our ability to obtain truly informed consent for participation in HIV vaccine trials.[13] The practical solution to this dilemma lies in a concerted effort to address both the basic research needs of better understanding how risks are perceived in general as well as applied research focused on understanding how potential subjects perceive the (uncertain) risks involved in participation in an AIDS vaccine trial.

This research would seek to extend ordinary thinking about "informed consent" in the context of IRB (Institutional Review Board) procedures. Rather than grounding judgments of the adequacy of disclosure of risks in the judgments of a group of fellow scientists, ethicists, and lawyers, this approach would seek to adduce the evidence necessary to ascertain whether the "facts" and the uncertainties concerning risks have in fact been communicated and understood by the various populations of potential subjects. This effort could proceed in parallel with collaborative efforts that involve representatives of the populations being recruited. It should be emphasized, however, that just as it would not be appropriate to assume that a group of independent scientists, ethicists, and legal experts could adequately vet the adequacy of a given risk communication, it is

equally the case that representatives of any population should not be assumed to be privy to the psychological processes that underlie the understanding, interpretation, and response of a population to a communication about the potential risks of participation in an HIV vaccine trial.

The approach we propose would not rely solely on the basis of expert judgment as to the objective accuracy of the proposed statements of risks. Rather, it would seek objective evidence that representative samples of the target population, on receipt of the proposed communication regarding the risks of participation in a trial, would demonstrate accurate and adequate comprehension of the risks entailed. This empirical test would require several types of contributions from behavioral and social scientists. Important examples include

- Ethnographic research to understand how persons in the social group or culture understand the concepts of risk, their preconceptions as to the nature of the risks entailed, and their perceptions (accurate or otherwise) of any constraints on their freedom to refuse participation
- Involvement of social scientists expert in risk perception in the development and evaluation of prototype communications regarding the risks and benefits of participation in the trials
- Iterative rounds of evaluation research to test the efficacy of alternative risk communications. This research would attempt to identify communications and clinical trial procedures that maximize the level of understanding of both the risks and uncertainties in our knowledge of these risks and that minimize the real and perceived threats to the voluntary nature of participation
- Research designed to understand the formal and informal networks that will disseminate information regarding the trials in the target populations and communities
- Collection of data for every recruited subject to document that risks are adequately understood prior to enrollment and that subjects choose to participate without any real or perceived coercion

While the foregoing is merely a thumbnail sketch of what would be required, it begins to address the types of behavioral and social research that should accompany any serious consideration of undertaking trials of HIV vaccines. There is a great potential for misunderstanding in this highly visible venture in risk taking that will be undertaken jointly by members of the populations at highest risk for HIV infection and by the scientists involved in designing and executing the trials. Subjects will face direct medical and social risks. For the scientists involved, the risks will be more indirect. (Reputations and the viability of this research endeavor could be threatened, if the trials were to go seriously awry.)

Some components of this risk are unavoidable—others are not. A *sine qua non* for avoiding recrimination in the event a trial were to go awry is the full disclosure of potential risks as well as disclosure of the uncertainties that attend to our understanding of those risks. Furthermore, subjects should be recruited in situations in which both in fact and in the subject's own perception there is complete freedom to refuse participation. As vaccine trials may be mounted in several quite different cultures around the world, it will be a nontrivial task to ensure that these conditions are met. We would suggest that this is, nonetheless, a crucial challenge, and one in which there are important tools and knowledge to be drawn from the social and behavioral sciences.

Adequate research must be conducted to communicate about the cognitively difficult topics of risk and of uncertainty in our judgments of risk. This research should not be an afterthought; rather it is central to discharging our ethical obligations to fairly communicate to subjects the risks of participation in order to obtain truly informed consent. The mere demonstration that subjects are exposed to a fair and truthful litany of potential risks (and benefits) does not satisfy this requirement. Rather we would argue that one must demonstrate that our subjects, in fact, have an understanding of these risks adequate to give informed consent. The latter demonstration might plausibly be provided by a parallel program of psychological research that elicits evidence that key aspects of the risk of the vaccine trials are, in fact, understood by representative samples of the research subjects.

We recognize that there may be some resistance to adding new research requirements to the threshold conditions for the launching of HIV vaccine trials. We would suggest, however, that there are many scenarios under which we would regret the decision to forego making this investment of time and resources. In the event a trial had unexpected adverse outcomes, the public might well ask whether the risk of such consequences was adequately understood by research subjects. In such a situation, our demonstrated commitment to conducting research to develop appropriate risk communications for each candidate population and the evidence that recruited subjects did have an appropriate comprehension of potential risks could be of great value. At a minimum, it might help assuage concerns that research subjects were misled.

Given the complex nature of the risks that must be explained, such evidence will be much more compelling to our fellow scientists and the public than mere knowledge that a given script was read to a subject and an appropriate form was signed. We would further suggest that while demonstrations of "understanding of risks" are not routinely required by IRBs today, it is not unlikely that scientific norms in this regard will shift over time. If this were so, compliance with a higher standard might help us avoid the situation that now confronts some scientists who conducted radiation research at midcentury. In this regard, we believe that developing better risk communications and assuring the adequacy of those communications are important but underappreciated areas in which behavioral and social scientists will make important contributions to the conduct of future trials of HIV vaccines.

MEASUREMENT OF BEHAVIORS THAT RISK EXPOSURE TO HIV

There will also be an important role for the behavioral and social sciences in measurement of the behaviors that risk HIV transmission. To ensure that a trial has adequate statistical power for the assessment of vaccine efficacy, it is necessary to recruit subjects whose past behaviors suggest that they will be at risk of future exposure to HIV. There is also a need to assess both the extent to which these behaviors change over time and the degree, if any, of systematic variation over time in the patterns of risk-related behavior in the control and experimental groups. Changes in behavior over time might occur, for example, if subjects responded to the counseling provided as part of the trial by altering their behaviors so as to reduce their risk of exposure to HIV. As Dr. Blower will discuss in her presenta-

tion, such changes would have the effect of decreasing the statistical power of the trial. Systematic variation in behaviors (across groups) might occur through inadvertent or deliberate "unblinding" of subjects' assignment into placebo or vaccine groups. Such "unblinding" need not be real, it need only produce a differential perception in the control and experimental groups of the likelihood that they were in one or the other group and this, in turn, would need to manifest itself in changes in risk behaviors. Clearly the monitoring of such behavioral changes will provide important ancillary data needed to interpret the results of any trial.

Because of the historic underinvestment in research on sexual behaviors,[14] there has been relatively little serious methodological research conducted on the impact of variations in question wording, mode of presentation, interview context, and other factors that can affect the validity and reliability of measurements of sexual behaviors. In the area of drug use, there is rather more methodological research, and some strong demonstrations that the nature of the interview context can powerfully affect the willingness of respondents to report use of illicit drugs. Experimental studies[15] embedded in large-scale surveys in the United States have found, for example, that use of self-administered questionnaires produces 2.4 times more reporting of cocaine use during the past month than interviewer questioning. There is also evidence (for other topics) that repeated questioning—as would occur in a vaccine trial—can induce changes in reporting and, perhaps, in behavior.[16]

Such findings begin to suggest the extent to which subjects' reporting of their sexual and drug use behaviors may be affected by the particular ways in which questions are worded and the situations in which they are asked. Navaline *et al.* have reported on their experiences using a computerized system that presents questions on a computer screen and accepts answers typed on the computer keyboard (without the intervention of an interviewer). There have been technological developments that may enable this technology to be used with populations that are insufficiently literate to respond to written questions. These new, computer-assisted procedures permit audio-administration of questions—thereby eliminating the requirement of respondent literacy.[17] The system of Navaline *et al.* and these new audio-questioning systems may prove useful in gathering sensitive information on sexual and drug use behaviors in trials of HIV vaccines.

These new technologies are but one example of the measurement tools available from research in the social and behavioral sciences. Basic and applied research is required to better understand

- The ways in which subjects structure their understanding of sexual and drug-taking behaviors
- The limits of their ability to provide accurate reports of past behaviors
- Their willingness to accurately report behaviors that may be stigmatized by the society or that may have been the subject of AIDS prevention messages (e.g., unprotected sexual contact)

and a host of related issues. Each of these factors will affect in a quite direct way the validity and reliability of behavioral measurements of risk exposure gathered at intake and during the course of HIV vaccine trials.

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Address reprint requests to:
Charles F. Turner
Program in Health and Behavior Measurement
Research Triangle Institute
6101 Executive Blvd.
Rockville, Maryland 20852