Resources and Needs of Research Ethics Committees in Africa: Preparations for HIV Vaccine Trials

BY CECILIA MILFORD, DOUGLAS WASSENAAR, AND CATHERINE SLACK

Research in developing countries is often financed by well-resourced, developed countries and conducted in vulnerable host communities with diverse cultural backgrounds. Moreover, multinational research is frequently conducted according to the regulatory frameworks of wealthier sponsor countries, which may be inappropriate to host country conditions and raise ethical concerns about potential exploitation of host communities and participants, insensitivity to community ethos, the scope of sponsor-investigator obligations, and the appropriate communication of research results to participants.

The capacity of research ethics committees (RECs) in developing countries to review research proposals is also a frequently cited problem. These RECs, which are required to interpret international ethics guidelines in specific socioeconomic and cultural conditions, often operate in complex environments characterized by power inequalities among government, funders, researchers, and/or communities. In addition to interests of government and other institutions, money, prestige, custom, or ignorance may influence ethical review, thereby compromising RECs’ independence, especially where it is difficult to challenge authority and debate complex issues. Developing country RECs may lack transparency, and conflicts of interest may be present. Self-appointed private commercial and noncommercial RECs may lack expertise, accountability, and open dialogue. Local expertise, technologies, and financial resources are often constrained.

There may be few trained and independent personnel in these regions to serve on committees, which could lead to bias and favoritism. High turnover of staff may impact continuity of expertise. These challenges, although relevant in developed country reviews, may be more extreme in developing country contexts.

HIV vaccine trials—which are often international collaborations between resource-poor nations and organizations drawn from more resourced countries—may be especially challenging to RECs in developing countries. These trials are designed to test safety, immunogenicity, and efficacy of candidate vaccines in preventing HIV infection (or disease) in healthy, uninfected volunteers. Early phase I

safety trials are conducted with small numbers of low-risk volunteers. Later phase II immunogenicity trials are conducted with larger numbers of volunteers, and phase III efficacy trials are conducted with thousands of volunteers at high risk of infection. All phases are randomized, placebo-controlled, and double-blinded. Host communities are often vulnerable due to poverty, illiteracy, and the stigma associated with HIV/AIDS. The ethical complexities of conducting HIV vaccine trials in developing countries include ensuring meaningful community participation; fair selection of volunteers; sound, culturally sensitive consent processes; monitoring of ongoing social harms; obligations of sponsors to ensure HIV treatment to volunteers who become HIV infected during trials in resource-poor contexts; and ensuring access to posttrial benefits, capacity development, and effective products.

In response to the complexities of conducting research in developing countries, numerous new initiatives are aimed at increasing capacity for ethical review of health research in such countries. These include funding from the WHO-UNAIDS African AIDS Vaccine Programme; the National Institutes of Health's Fogarty International Center, the South African Research Ethics Training Initiative (SARETI); the International Research Ethics Network for Southern Africa (IRENSA); the NIH Department of Clinical Bioethics; the Wellcome Trust; the European Commission; the Global Bioethics Forum; and the World Health Organization (WHO). The Pan African Bioethics Initiative (PABIN) aims to support capacity and networking in research ethics in Africa, and the African Malaria Network Trust (AMANET) has been building capacity for African RECs involved in malaria research. A recent European Union (EU) initiative (Networking for Ethics on Biomedical Research in Africa—NEBRA) aims to enhance ethics review capacity in West Africa.

Despite these initiatives, little empirical research has been conducted in developing countries to determine REC capacity to review and approve clinical trial protocols, including protocols for HIV vaccine trials. Research to date reveals the need to develop appropriate local ethical guidelines and policy, to train REC members, and to increase REC independence, diversity of membership, and monitoring of approved protocols. Other studies indicate that RECs are concerned about the cultural appropriateness of studies, relevance of the research to the host country, and a need for local language consent forms. One study found that developing country researchers believed that RECs were more concerned with politics than with protecting the interests of research participants.

With regard to HIV vaccine research, researchers in Uganda report many social, political, legal, ethical, and behavioral barriers. These include public misconceptions and media misinformation, lengthy review process, and inadequate national regulatory mechanisms. In Kenya, reviewers report that they often do not have the training to understand complicated immunology concepts. In general, African ethics reviewers state that lengthy protocols, monitoring protocols, and inadequate funding and ethics capacity training make review difficult.

The purpose of our study was to identify perceived resource and capacity building needs of African RECs for the review of HIV vaccine trial protocols. Results should inform the development of focused and cost-effective training initiatives and related research to support protocol review of HIV vaccine trials. Debate of the ethical issues raised by the RECs is beyond the scope of this article.

Study Methods

Fifteen African countries with identifiable RECs were selected according to their involvement or planned involvement in HIV vaccine trials. At the time our study was conducted, both Uganda and Kenya had already conducted HIV vaccine trials. Botswana was preparing for its first trial (which began in June 2003). South African committees were reviewing initial protocols (approved in September 2003). Tanzania and Cote d'Ivoire had national AIDS vaccine plans. Ethiopia, Senegal, Zambia, Nigeria, Zimbabwe, Malawi, Cameroon, Burkina Faso, and The Gambia were all at different levels of trial preparedness.

Contact details of all RECs in the above-mentioned countries were obtained via snowball sampling. Over 300 potential sources from workshops, web searches, and the U.S. Office for Human Research Protections (OHRP) were contacted to assist with the identification of African RECs. Details were verified for a total of 71 RECs in the 15 selected African countries.

This study was approved by the University of KwaZulu-Natal's Nelson R. Mandela School of Medicine ethics committee, a local REC. Details of respondent RECs and the countries from which they originated were to be kept confidential in public reports on findings. Confidentiality was assured to enhance accuracy of reporting without fear of publicly being seen as underresourced or lacking capacity to review large international studies. Assuring confidentiality also prevents adverse perceptions of host institutions and national competencies. In keeping with this agreement, our study reports only regional summaries, rather than specific REC or national data.

Self-administered questionnaires
were compiled, drawing on existing scales for self-audit of RECs, including the European Guidelines for Auditing Independent Ethics Committees\(^{38}\) and the Quality Assurance Self-Assessment Tool.\(^{39}\) Additional items were based on challenges identified in the literature. The questionnaire, which is available on request from the authors, consisted of 40 main questions and eight sections (demographics; training; guideline use; REC procedures; laws regulating research; financial and material resources; affiliation; and committee composition). A detailed information sheet informed potential respondents of the aims, risks, benefits, confidentiality, outputs, feedback, and sponsors of the study. Completion of the questionnaire was taken as an indication of consent. No incentives were provided for this study apart from a guarantee of feedback and the indirect prospect of further training, which may have increased response rates.

The questionnaires (English or French) were distributed in late 2002 and early 2003 to chairpersons and/or administrators of 71 RECs. Follow-up telephone calls were made to all contacts to ensure they had received the questionnaire. Questionnaires were redistributed as necessary. Reminder telephone calls were made to those contacts that had requested them.

Either the REC chair or administrator completed all questionnaires, though it is not clear whether they were completed individually or in a group setting. The quantitative data set was analyzed using basic descriptive statistics. Responses to open-ended questions were extracted, coded, and summarized. Each respondent REC was sent a confidential copy of its individual data superimposed on a summary result. This served to verify the analysis and enabled each respondent to compare his or her committee’s profile relative to the whole sample.

**Study Results**

Regional results are presented as percentages to facilitate regional comparisons. However, because of the low number of respondents, exact numbers are also given. Findings specific to HIV vaccine trial protocol review are specified as such. Other results apply to ethical review in general. For the purposes of this research, Southern Africa comprises South Africa, Zimbabwe, Botswana, Zambia, and Malawi; West Africa comprises Nigeria, The Gambia, Senegal, Cote d’Ivoire, Cameroon, and Burkina Faso; and East Africa is Tanzania, Uganda, Ethiopia, and Kenya. Results are presented either as a summary of the whole sample or regionally for either Southern, East, or West African RECs.

There was a 61% response rate (n=43), but 11% (n=8) of those who responded declined to complete the questionnaire. This response rate is considered good for mail surveys that do not undertake efforts to increase responses.\(^{40}\) Reported reasons for noncompletion of the questionnaire included perceived lack of involvement in HIV vaccine trials (n=3, 4%), incomplete formation/inactivity of RECs (n=3, 4%), and concerns about confidentiality (n=2, 3%). No further explanations were sought. Two national RECs failed to respond despite numerous follow-ups. The results thus depict 35 RECs from 13 African countries.

The highest response rate was from West Africa (60%, n=6), followed by Southern Africa (54%, n=19) and East Africa (38%, n=10). Because the highest numbers of respondents were from Southern Africa, regional analyses may be skewed. However, percentages are included in an attempt to make these results more relevant.

The results reflect the self-perceived capacity of RECs to review HIV vaccine trial protocols. Due to the length of the questionnaire and the complexity of the data, this article focuses only on the structure, function, and independence of RECs, perceived capacity, training needs in relation to HIV vaccine trials, usefulness of guidelines, and resources.

**Structure and Functions of Committees.** Medical doctors (40%, n=185) formed the bulk of REC members, with ethicists (1%, n=4) being underrepresented. There were very few lawyers (6%, n=27) or community members (7%, n=30). The remaining committee members included scientists (19%, n=89), nurses (8%, n=39), religious leaders (4%, n=19), and other undefined personnel. On average, respondent RECs reviewed eight protocols per meeting, with a range from zero to more than 40 per meeting. Thirty-four percent (n=11) of respondent RECs meet monthly, whereas a quarter (n=8) reported meeting on an ad hoc basis.

**Financial and Material Resources.** A third of RECs (32%, n=10) reported they received funding, whereas RECs in six of the 12 countries represented had no access to funding. Forty-two percent (n=5) of those RECs that had reviewed HIV vaccine trial protocols received some funding compared with 38% (n=5) of those committees that had not reviewed these types of protocols. At a regional level, 44% (n=8) of RECs in Southern Africa, 25% (n=1) in West Africa, and 11% (n=1) in East Africa reported receiving funding, which came either from levying a review fee, from government, from the affiliated university or institution, or from pharmaceutical companies.

RECs were asked about their access to infrastructure. Although most had access to some resources, over 40% (n=13) did not have dedicated office space. Many only had access to computers, email, and the Internet through institutional and personal support. Two thirds (n=20) had administrative support, an important resource. Almost 42%
(n=5) of RECs with no office space reported limited or no capacity to review HIV vaccine protocols compared with 2.8% (n=4) of those that did have office space. Of those that had no secretarial support, 50% (n=5) reported limited to no capacity, compared with 21% (n=4) of RECs that had secretarial support. In general, those committees that had reviewed HIV vaccine trial protocols were better resourced than those that had not. Also, the Southern region was best resourced, followed by East Africa, with West Africa having the greatest infrastructure needs.

Perceived Independence.

When asked whether they believed that RECs in their countries were truly independent, 65% (n=20) responded favorably. Ten percent (n=3) said that some RECs were not truly independent, whereas the remainder were uncertain. Almost 79% (n=15) of RECs with dedicated office space felt that the RECs in their countries were truly independent. In contrast, 58% of RECs without dedicated office space felt that RECs were not truly independent.

Respondents were asked to indicate whether listed factors were challenges to the independence of their committees (Table 1). The most common reported challenge to independence was pressure from sponsors (28%, n=9). Almost 13% (n=4) reported pressure from political powers. There were also perceptions of biased committee members (9%, n=3) and lack of transparency of RECs (6%, n=2). There was one report of bribery and another of unequal treatment of applicants in the review process.

Ethical Guidelines and Legislative Frameworks.

Respondents were asked to rate the appropriateness of a list of international ethical guidelines for use in their country. Ratings were very appropriate, somewhat appropriate, not really appropriate, or very inappropriate. The UNAIDS guidelines on HIV vaccine research were rated as very appropriate by 67% (n=18) of respondents. Of the RECs that had actually reviewed HIV vaccine protocols, all but one gave the UNAIDS guidelines the highest rating. Fifty-eight percent (n=18) of respondents said the Declaration of Helsinki guidelines were very appropriate, whereas 48% (n=14) rated the CIOMS guidelines as very appropriate. The Belmont Report ranked lowest. All committees that had actually reviewed HIV vaccine trial protocols felt that all guidelines listed were very appropriate for use in their countries.

Eighty-four percent (n=30) of respondents said that developing appropriate national guidelines was a priority. The variable use of ethical guidelines across committees, insensitivity to local conditions, and the difficulty of adapting international guidelines to local conditions were all rated as important challenges to the use of guidelines by 70% (n=23) of respondents. A total of 28 RECs from 13 countries indicated that they would value assistance in adapting the UNAIDS HIV vaccine trial guidelines for local conditions. Knowledge of local legal frameworks governing research was inconsistent and unclear.

Perceived Capacity to Review HIV Vaccine Trial Protocols.

RECs were asked to rate their perceived capacity to review protocols for HIV vaccine trials on a rating scale of "excellent-good-moderate-limited-no capacity." Capacity was not defined. Of the 81% (n=26) of respondents RECs that had reviewed clinical trial protocols, 38% (n=12) said they had reviewed protocols for HIV vaccine trials. However, 66% (n=21) reported that they would be reviewing such protocols in the future.

RECs reported varying levels of perceived capacity to review HIV vaccine trial protocols. Only one REC reported excellent capacity to review these protocols. Forty-three percent (n=13) reported moderate capacity to review these protocols, whereas almost a third (30%, n=9) reported limited to no capacity. Significantly, more than 70% (n=22) reported moderate, limited, or no capacity to review HIV vaccine trial protocols.

Of the RECs that had experience reviewing protocols for HIV vaccine trials, 45% (n=5) reported that they had good to excellent capacity to review such protocols, whereas 18% (n=2) felt they had limited capacity to do so. Of the RECs that did not have such experience, 21% (n=3) said they had good to excellent capacity to review protocols for HIV vaccine trials. All RECs, except the one that reported excellent capacity, agreed that a lack of training in ethics applied to HIV vaccine trials was a challenge.

| Table 1. Perceived Challenges to Independence of RECs |
|------------------------------------------|----------|----------|----------|
| **Issues**                               | **Agree**| **Disagree**| **Uncertain** |
| Pressure from sponsors                   | 28% (n=9) | 63% (n=20) | 9% (n=3)   |
| Pressure from political powers           | 13% (n=4) | 75% (n=24) | 12% (n=4)  |
| Biased committee members                 | 9% (n=3)  | 72% (n=23) | 19% (n=6)  |
| Lack of transparency of RECs             | 6% (n=2)  | 75% (n=24) | 19% (n=6)  |
| Offers of favor/money to RECs            | 3% (n=1)  | 81% (n=26) | 16% (n=5)  |
| Unequal treatment of applicants in review| 3% (n=1)  | 84% (n=27) | 13% (n=4)  |
Regional differences emerged in reported capacity to review protocols for HIV vaccine trials. Overall, self-reported capacity for the excellent to good range was higher in some REC's in Southern and East Africa than in West African REC's. Thirty percent (n=5) of REC's in Southern Africa, 33% (n=3) in East Africa, and no West African REC's reported good or excellent capacity to review HIV vaccine trial protocols. For the moderate to limited range, 50% (n=2) of West African REC's reported moderate capacity and 50% (n=2) reported limited capacity. For Southern African REC's, 53% (n=9) reported moderate capacity and 18% (n=3) reported limited capacity. Moderate review capacity was reported by 22% (n=2) of East African REC's, and limited capacity by 33% (n=3). The only region with REC's reporting no capacity to review HIV vaccine trial protocols was East Africa (n=1, 1%).

**Perceived Training Needs.**

Less than half (40%, n=49) of all members received ethics training prior to joining their committees, while just over half (52%, n=69) had received training after assuming their position on the committees. Although 29% (n=6) of chairs received some training in ethics involving HIV vaccine research, only 6% of ordinary members had received any training in this area.

Respondents rated the importance of 20 listed training needs as very important, quite important, not so important, or unimportant. At least 60% of REC's viewed all training needs issues as important overall (combined ratings of very important and quite important), though at least 90% agreed on the importance of eight training needs: 1) scientific aspects of HIV vaccine trials; 2) determinations to run phases; 3) potential risks of HIV vaccine research; 4) appropriate risk reduction techniques; 5) posttrial access to benefits; 6) placebo-controlled trials; 7) monitoring and oversight; and 8) vaccine product not meeting prevailing subtype (clade) (Table 2).

Even REC's that have reviewed HIV vaccine trial protocols viewed these issues as important, with 100% of these REC's identifying scientific trial issues and determinations to run phases as important training needs. Other scientific aspects, such as placebo-controlled trials and the clade of the vaccine, were viewed as important by 92% (n=11) and 90% (n=12), respectively of the committees that had reviewed protocols for HIV vaccine trials. Monitoring and oversight (91%, n=10) and social and behavioral studies (92%, n=9) were also rated as important by a high proportion of the committees. The issues that received lower rankings by REC's overall included the selection of minors as subjects (75%, n=24), community participation (69%, n=20), and privacy and confidentiality (60%, n=18). Of the committees with experience reviewing HIV vaccine trials, 55% (n=6) said that privacy and confidentiality were important for training, and 50% (n=5) said the same for community participation (Table 2).

A few committees rated some issues as unimportant. These included participant selection in vulnerable populations (n=2), women (n=2), and minors (n=2); assessment of understanding in informed consent (n=2); community participation (n=2); access to treatment for HIV infection (n=1); privacy and confidentiality (n=1); cultural sensitivity to informed consent (n=1); placebo-controlled trials (n=1); and incentives for participation (n=1). It is not clear whether an “unimportant” rating demonstrated that these REC's have adequate training in such issues, or whether they are unaware of the significance of such issues.

**Challenges to REC's.**

Respondents were also asked whether they agreed or disagreed that certain general issues presented challenges. Overall, 97% (n=30) agreed that committee members had inadequate training in the ethics of HIV vaccine trials. Slightly fewer REC's that had reviewed HIV vaccine trial protocols (91%, n=10) agreed. Over 87% (n=27) of all respondents and 73% (n=8) of those that had reviewed HIV vaccine trial protocols agreed that there was a lack of general and sufficient ongoing training for members in health research ethics. Seventy-five percent (n=24) of all respondents agreed that competence to review HIV vaccine trial protocols presented a challenge, whereas 64% (n=7) of those that had reviewed these protocols agreed. Overall, 86% (n=25) of respondents agreed that they had inadequate ability to monitor approved protocols. A higher proportion of REC's that had actually reviewed HIV vaccine trial protocols (91%, n=10) agreed that monitoring approved protocols was a challenge (Table 3).

**Discussion.**

In this study, we examined membership, structure, and training characteristics of REC's in 13 African countries, as well as REC perceived training and capacity building needs. The general finding from this study is that African REC's view their capacity to review HIV vaccine trial protocols as "moderate to limited," though the rating was more optimistic among committees that had experience reviewing such protocols. Intuitively, the overall reported moderate to limited capacity to review protocols for HIV vaccine trials appears consistent with reported inadequate access to infrastructure and limited funding. Moreover, this self-reported capacity could also be related to the fact that of 152 members of the respondent REC's, only seven (5%) reported receiving training in the ethics of HIV vaccine trials.

Training in "scientific aspects" was identified as the most pressing capacity building need. This matches reported experiences of African committees and the complexities of
**Table 2. Perceived Training Needs**

<table>
<thead>
<tr>
<th>Training needs</th>
<th>Overall</th>
<th>Southern</th>
<th>East</th>
<th>West</th>
<th>Had not reviewed HIV vaccine trial protocols</th>
<th>Had reviewed HIV vaccine trial protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific design issues</td>
<td>97% (n=31)</td>
<td>100% (n=18)</td>
<td>100% (n=9)</td>
<td>75% (n=4)</td>
<td>95% (n=19)</td>
<td>100% (n=12)</td>
</tr>
<tr>
<td>Determinations to run phases</td>
<td>97% (n=28)</td>
<td>100% (n=16)</td>
<td>88% (n=7)</td>
<td>100% (n=5)</td>
<td>94% (n=17)</td>
<td>100% (n=11)</td>
</tr>
<tr>
<td>Potential risks of HIV vaccine research</td>
<td>97% (n=31)</td>
<td>94% (n=17)</td>
<td>100% (n=9)</td>
<td>100% (n=5)</td>
<td>100% (n=20)</td>
<td>83% (n=11)</td>
</tr>
<tr>
<td>Appropriate risk reduction techniques</td>
<td>94% (n=30)</td>
<td>94% (n=17)</td>
<td>88% (n=8)</td>
<td>100% (n=5)</td>
<td>100% (n=20)</td>
<td>83% (n=10)</td>
</tr>
<tr>
<td>Post trial access to benefits</td>
<td>94% (n=29)</td>
<td>89% (n=15)</td>
<td>100% (n=9)</td>
<td>100% (n=5)</td>
<td>100% (n=19)</td>
<td>83% (n=10)</td>
</tr>
<tr>
<td>Placebo controlled trials</td>
<td>91% (n=29)</td>
<td>84% (n=15)</td>
<td>100% (n=9)</td>
<td>100% (n=5)</td>
<td>90% (n=18)</td>
<td>92% (n=11)</td>
</tr>
<tr>
<td>Monitoring and oversight</td>
<td>90% (n=28)</td>
<td>82% (n=14)</td>
<td>100% (n=9)</td>
<td>100% (n=5)</td>
<td>90% (n=18)</td>
<td>91% (n=10)</td>
</tr>
<tr>
<td>Vaccine products not prevailing clade</td>
<td>90% (n=27)</td>
<td>88% (n=15)</td>
<td>100% (n=9)</td>
<td>75% (n=3)</td>
<td>89% (n=16)</td>
<td>92% (n=12)</td>
</tr>
<tr>
<td>Access to treatment for HIV infection</td>
<td>87% (n=27)</td>
<td>76% (n=13)</td>
<td>100% (n=9)</td>
<td>100% (n=5)</td>
<td>89% (n=17)</td>
<td>83% (n=10)</td>
</tr>
<tr>
<td>Potential benefits of HIV vaccine research</td>
<td>87% (n=27)</td>
<td>82% (n=14)</td>
<td>100% (n=8)</td>
<td>100% (n=5)</td>
<td>94% (n=17)</td>
<td>83% (n=10)</td>
</tr>
<tr>
<td>Social and behavioral studies</td>
<td>86% (n=25)</td>
<td>75% (n=12)</td>
<td>100% (n=8)</td>
<td>100% (n=5)</td>
<td>84% (n=16)</td>
<td>90% (n=9)</td>
</tr>
<tr>
<td>Interpretation of preclinical studies</td>
<td>84% (n=27)</td>
<td>72% (n=13)</td>
<td>100% (n=9)</td>
<td>100% (n=5)</td>
<td>90% (n=18)</td>
<td>75% (n=9)</td>
</tr>
<tr>
<td>Subject selection: vulnerable populations</td>
<td>84% (n=26)</td>
<td>76% (n=13)</td>
<td>89% (n=8)</td>
<td>100% (n=5)</td>
<td>84% (n=16)</td>
<td>83% (n=10)</td>
</tr>
<tr>
<td>Assessment of cultural sensitivity to consent</td>
<td>81% (n=25)</td>
<td>70% (n=12)</td>
<td>89% (n=8)</td>
<td>100% (n=5)</td>
<td>80% (n=16)</td>
<td>82% (n=9)</td>
</tr>
<tr>
<td>Incentives for participation</td>
<td>77% (n=24)</td>
<td>65% (n=11)</td>
<td>89% (n=8)</td>
<td>100% (n=5)</td>
<td>84% (n=16)</td>
<td>67% (n=8)</td>
</tr>
<tr>
<td>Subject selection: women</td>
<td>77% (n=24)</td>
<td>70% (n=12)</td>
<td>78% (n=7)</td>
<td>100% (n=5)</td>
<td>84% (n=16)</td>
<td>67% (n=8)</td>
</tr>
<tr>
<td>Assessment of understanding for informed consent</td>
<td>77% (n=24)</td>
<td>65% (n=11)</td>
<td>88% (n=8)</td>
<td>100% (n=5)</td>
<td>84% (n=16)</td>
<td>67% (n=8)</td>
</tr>
<tr>
<td>Subject selection: minors</td>
<td>75% (n=24)</td>
<td>61% (n=11)</td>
<td>89% (n=8)</td>
<td>100% (n=5)</td>
<td>80% (n=16)</td>
<td>67% (n=8)</td>
</tr>
<tr>
<td>Community participation</td>
<td>69% (n=20)</td>
<td>60% (n=9)</td>
<td>66% (n=6)</td>
<td>100% (n=5)</td>
<td>79% (n=15)</td>
<td>50% (n=5)</td>
</tr>
<tr>
<td>Privacy and confidentiality</td>
<td>60% (n=18)</td>
<td>56% (n=9)</td>
<td>44% (n=4)</td>
<td>100% (n=5)</td>
<td>63% (n=12)</td>
<td>55% (n=6)</td>
</tr>
</tbody>
</table>

HIV vaccine development. Research that lacks scientific validity is de facto unethical insofar as it exposes participants to risks and inconveniences for no purpose. Therefore RECs should be assured that research protocols are scientifically valid either via their own review or that of some other body. However, "scientific aspects" is a broad, unrefined category that could encompass the design of candidate vaccines (e.g., to evaluate risks to volunteers) or the clinical trial itself. It may exclude "scientific" issues, such as interpretation of preclinical studies and clade issues, which were rated as important by slightly fewer RECs (84%, n=27 and 90%, n=27, respectively). The relative importance of this issue could be related to the fact that many of the REC members have scientific backgrounds. It is necessary to explore in greater detail those scientific aspects that challenge RECs, perhaps in future workshops or research.

Making determinations to run trial phases was reported as a critical training need by many RECs. This might reflect anxiety around evaluating safety and immunogenicity data to determine whether efficacy trials...
Table 3.

<table>
<thead>
<tr>
<th>Issue</th>
<th>Overall</th>
<th>Had reviewed HIV vaccine protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of training: HIV vaccine trial ethics</td>
<td>97% (n=30)</td>
<td>91% (n=10)</td>
</tr>
<tr>
<td>Lack of ongoing training: Health research ethics</td>
<td>87% (n=27)</td>
<td>73% (n=8)</td>
</tr>
<tr>
<td>Lack of training: Health research ethics</td>
<td>87% (n=26)</td>
<td>80% (n=8)</td>
</tr>
<tr>
<td>Inadequate ability to monitor approved research protocols</td>
<td>80% (n=25)</td>
<td>91% (n=10)</td>
</tr>
<tr>
<td>Competence to review HIV vaccine trial protocols</td>
<td>75% (n=24)</td>
<td>64% (n=7)</td>
</tr>
</tbody>
</table>

are needed. Furthermore, it is often not clear whether trial phases should be implemented in both sponsor and host country or host country alone; or whether phase I/II trials that have been conducted in one country should necessarily be repeated in the community or country in which phase III trials are to be conducted. Recs also expressed the need for training in potential risks of HIV vaccine trials and appropriate harm minimization measures. Estimating the likelihood and magnitude of risks is a notoriously difficult task routinely expected of RECs. HIV vaccine trials pose physical and psychosocial risks for individuals and host communities ranging from unexpected side-effects to potential stigma and discrimination. The intensity and scope of harm minimization obligations are the subject of some debate.

Training in posttrial access to benefits was also perceived as important. RECs may need better guidance in evaluating claims of potential benefits, including access to knowledge/results (in early trials) or to a product proven beneficial (in later trials). The latter is consistent with other developing country research and reveals the problems of determining whether access to products should be limited to trial subjects and who will pay for post-trial access. Posttrial benefits may include capacity development or technology and intellectual property and have been the subject of debate surrounding Tenofovir and anti-AIDS drugs being tested in clinical trials in Asia and Africa. These results are consistent with responses of RECs that had reviewed HIV vaccine trial protocols, as were results regarding training in scientific design issues and determination to run phases.

At a regional level, fewer Southern African respondents reported problems with training than East or West African RECs. This may reflect a generally more resourced setting. The fact that West African RECs viewed no issue as unimportant suggests that REC capacity building programs in West Africa should be comprehensive. Although we found higher levels of ethics training than reported in previous research in selected African and some other developing countries, it is striking how little training members receive after they start serving on an REC. Our findings indicate a need for general research ethics training for all committee members, and for specific training in HIV vaccine research. Previous research has recommended a focus on conceptual rather than procedural issues in training.

Other studies also report perceived and actual lack of independence of certain RECs. Overall, respondents in our study indicated they believed their RECs were truly independent, though they did identify some challenges to their independence. The RECs in our sample may indeed be independent of external influences, though it is also possible that respondents are not aware of these sensitive issues. The fact that RECs from West African countries did not perceive any factors as a challenge to their independence warrants closer investigation.

Poor funding for RECs could have several implications, including inadequate ability to monitor approved research and poor infrastructure for effective protocol review. The lack of dedicated offices and support for RECs may be a challenge to the functioning and independence of RECs. Underfunding suggests that ethical review may not be regarded as a core component of research. For ethics to be taken seriously, REC funding should be proportional to the funding of the scientific costs of the trials under review. Careful attention needs to be given to who funds research (government, research institutions, or fees) in order to preserve independence.

Limitations of Study

We note several limitations to this study. First, self-report is subject to possible bias. The RECs that responded to our survey may have favorable records and their responses may be in the direction of overreporting resources and safety mechanisms. Alternatively, respondents may overreport their needs and capacity constraints in an attempt to secure funding. Furthermore, this was exploratory research and the questionnaire was not statistically validated. However, it elicited important descriptive data on resources available to African RECs. Another limitation is that respondents were asked to provide
details of all their committee members. The fact that one member responded on behalf of all members may have influenced the accuracy of the results.

The proportionally higher number of RECs in Southern Africa may have introduced a regional response bias. However, this is also indicative of the regional strength and proportional presence of RECs in Southern Africa. Furthermore, some responses might reflect low ethical sensitivity rather than the absence of challenges. This study was not equivalent to an audit, which might be a more accurate though costly way of verifying the reported data. However, it provides preliminary data to focus on in more detailed research.

Although the study may have promoted some reflection on ethical issues, this cannot be verified, as it was not asked. The questionnaire did not ask about the extent to which RECs network with each other. Networking could facilitate capacity building through learning from each other’s experiences. The questionnaire itself is unlikely to have promoted networking, although all respondents were invited to make use of the contacts list we posted on the Internet. We have no record of how many RECs actually did so.

Conclusions and Recommendations

That African RECs rated their own capacity to review HIV vaccine protocols as “moderate to limited” suggests that these RECs could benefit from initial and ongoing training. We recommend that training for review of HIV vaccine trials emphasize the ability of RECs to evaluate scientific issues in HIV vaccine development and testing and to make complex risk-benefit determinations. Despite the emphasis on informed consent in the literature, consent issues were ranked relatively low by respondents. In order to obtain a rich sense of particular demands, trainers should elicit case examples from attendees prior to workshops.

Although the results from our study depict resources and needs mainly in relation to HIV vaccine research, they may apply more broadly to all HIV prevention research in developing countries. RECs have an underlying need for sound ethics training. While there is a need for ethics training applied to HIV vaccine trials, generic ethics training needs could also be addressed by ethics initiatives and sponsors of ethics training programs. Various global sponsors of research ethics training in Africa should coordinate their efforts to ensure that training suits real needs and reaches appropriate individuals. While not addressed by our study, there is the possibility that a few relatively well-placed REC members are accessing repeated training opportunities with little net gain to overall review capacity where it is most needed.

Despite the efforts of many ethics training programs, there remains an unclear what impact these programs have had on REC ethics reviews, especially for reviews of protocols for HIV vaccine trials.

Our findings also suggest that other interventions apart from training per se would assist RECs in their core business of protocol review. These include ensuring that RECs have mechanisms for ongoing monitoring of approved protocols, assistance to negotiate with institutions regarding financial support for the REC, support to manage pressure from sponsor institutions, and assistance with developing appropriate national ethical guidelines for HIV vaccine development. We hope that data from the present study will assist with the development of focused and cost-effective initiatives to resource these RECs, as well as give direction for future research.

Acknowledgments

We thank Ann Strode for contributions to the research, Naseer Khan for data management, and Graham Lindegger for comments on the manuscript. We also thank all the respondents. The comments of the 2003 SARETI students are also valued.

This work was funded by the UNAIDS/WHO HIV Vaccine Initiative (HVI) and the African AIDS Vaccine Programme (AAVP). This research was approved by a local ethics committee and the Nelson R. Mandela School of Medicine Research Ethics Committee at the University of KwaZulu-Natal, South Africa.

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12. See ref. 7, Ofomi-Anyinam 2001; see ref. 11, Nuffield Council 2002.
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33. See ref. 32, Karasani 2003.
37. Contact details were placed on the following website: http://www.saaiv.org.za/inventory.htm.
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45. See ref. 15, UNAIDS 2000.
46. See ref. 29, Mugerwa et al. 2002.
49. See ref. 15, UNAIDS 2000.
54. See ref. 27, Hyder et al. 2004; see ref. 24, Kim et al. 2003.
58. See ref. 25, Kass et al. 2003.
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61. See ref. 11, Nuffield 2002.
62. See ref. 48, Emanuel et al. 2000.
Part III: Meeting the Challenge When Data Sharing Is Required

In this final article of our three-part series, we describe some approaches that can be used in meeting the challenges posed by the sharing of confidential data. First, we provide an overview of two basic methods of protecting the confidentiality of data. Next, we look specifically at data sharing agreements. The last section summarizes issues to be considered by Institutional Review Boards (IRBs) and research administrators, who would not be expected to master these methods, but should be aware of them.

Basic Methods of Assuring Confidentiality

U.S. federal statistical agencies, such as the U.S. Census Bureau and the National Center for Health Statistics, have established practices and procedures that enable others to access and use the data that government agencies collect. Their goal is to provide useful statistical information to data users while assuring that the responses of individuals are protected. Over the past twelve years, several groups have examined the role of the federal government as a “data steward” and summarized its contributions, including the Panel on Confidentiality and Data Access, the Federal Committee on Statistical Methodology’s (FCSM) Subcommittee on Disclosure Limitation, and FCSM’s Confidentiality and Data Access Committee (CDAC).

The Panel on Confidentiality and Data Access provided generic labels for the two methods that U.S. federal statistical agencies use to protect the confidentiality of data they collect. These are:

- **Restricted data**: Any of a variety of techniques may be used to restrict the content of the data prior to releasing it to the general public. These techniques are called statistical methods to limit disclosure, statistical disclosure avoidance techniques, or statistical disclosure control methods.
- **Restricted access**: Techniques to restrict the conditions of data access; i.e., who can have access to the data, at what locations, under what protections, with what supervision, and for what purposes.

Many forms of data are shared, including instruments and instructions required to conduct the research. For the purposes of this section we will define data to mean the final research data, which are usually in electronic form. Final research data mean the recorded factual material that was the basis of the research publication and the documentation of those data. This is very similar to the definition of data used by the National Institutes of Health (NIH) in its data sharing guidance. Such data are frequently shared as a computerized file, called microdata, that consists of individual records, each containing values of variables for a single person, household, business establishment, or other unit.

It is beyond the scope of this article to discuss evaluation of disclosure risk of qualitative data such as videotapes, field notes, or case records. Typically, however, such data are not appropriate for public-use sharing and need to be shared with qualified individuals under a restrictive data sharing agreement, as discussed later in this article.

Restricted Data

Data may be restricted in many ways, yielding a wide range of data products that vary in usefulness to secondary users. There is always a trade-off between disclosure risk and data usefulness to secondary analysts. Summarizing briefly, some of these methods are: deleting some variables; recoding categorical variables into larger categories; rounding or truncating continuous variables; “masking” outliers; and enlarging geographical areas. Under certain circumstances more statistically sophisticated methods may be employed, such as adding “noise” to the data, data swapping, rank swapping, and blurring.

The type of data product to be released dictates the choice of methods used to limit disclosure. Most quantitative data are released as either tables or microdata.
files. In Part II, we presented an extensive discussion of disclosure limitation techniques for electronic data. Nonquantitative data, such as ethnographies and case studies, also may contain data tables and descriptions that may allow reidentification. The following brief description of methods to reduce the disclosure risk in tables is relevant to both quantitative and qualitative data.

Restricting Tabular Data. The key issue in restricting the data in a table is to determine what is a statistically “sensitive” cell. Two kinds of rules are used to identify sensitive cells:

- Threshold rule: A cell is sensitive if the number of respondents is less than some specified number. Thus, if a researcher or statistical consultant decides that all cells in a table must have at least five cases (e.g., of HIV infection), then a cell with only two cases in a county would be “sensitive.”

- Dominance rule: A cell is sensitive if a small number of respondents contribute a larger percentage of the total value of a cell (e.g., one establishment employs over 80% of the people in a certain industry in a given county).

Sensitive cells are usually protected via suppression—they are not published or shared. Rather, the categories containing sensitive data are broadened to increase cell size, the geographic locations containing sensitive cells are eliminated (or in the case of qualitative data, carefully disguised), or the cells themselves are simply eliminated. Suppression of sensitive cells is called primary suppression.

When a table has a primary suppression and also contains row and column totals, then each row and column must have at least two suppressed cells; otherwise an intruder could sum the cell values and subtract from the row or column total to obtain the value of the sensitive cell. Secondary suppressions are nonsensitive cells that are selected for suppression to assure that the respondent level data in sensitive cells cannot be estimated accurately.

Selection of the appropriate data restriction method depends on the nature of the data and on the vulnerabilities of the respondents and the research institution. How much risk of reidentification can the respondents and the research institution tolerate? No restricted data method is entirely without risk. The only way to avoid disclosure risk completely is not to share or release data—to the detriment of all research.

For that matter, it is useful to recognize that long before the data are shared they are vulnerable to the risk

### Table 1.

**Glossary of Key Terms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Confidentiality</td>
<td>The treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding of the original disclosure.** Uses that are not consistent with the original understanding require a new permission.</td>
</tr>
<tr>
<td>Data archive</td>
<td>A data &quot;library&quot; that stores the data, typically in electronic form.</td>
</tr>
<tr>
<td>Data documentation</td>
<td>A description of the data that instructs secondary users on how the data were obtained, how the variables are defined, how the data were cleaned and analyzed, and any other details that would be needed to make accurate use of the data.</td>
</tr>
<tr>
<td>Data enclave</td>
<td>A place where identifiable, sensitive, or irreplaceable data or artifacts may be used under conditions of supervision and limited access.</td>
</tr>
<tr>
<td>Nondisclosure methods</td>
<td>Restriction of data or access to data to minimize risk of identification.</td>
</tr>
<tr>
<td>Restricted data techniques</td>
<td>Techniques that may be used to restrict the content of the data prior to releasing it to the general public.</td>
</tr>
<tr>
<td>Restricted access</td>
<td>Techniques to restrict the conditions of data access; i.e., who can have access to the data, at what locations, under what protections, with what supervision, and for what purposes.</td>
</tr>
<tr>
<td>Statistical disclosure limitation</td>
<td>The application of statistical techniques to transform data to limit the risk of disclosure. Some techniques are designed for data in tabular form, others for microdata. (Also called statistical disclosure avoidance, statistical data protection, or statistical disclosure control.)</td>
</tr>
</tbody>
</table>


** See Part I, Table 1 for additional definitions.
that the investigator or research assistants will discuss their interesting cases with others in a way that leads to identification of the individuals in those cases. As in all other kinds of risk assessment, there are always ambient, everyday risks that must be considered and dealt with.

Three-Pronged Approach for IRBs. Knowledge of statistical methods to limit disclosure is not normally within the scope of an IRB’s expertise. However, IRBs must be assured that appropriate steps have been taken to deidentify tabular or electronic data. We suggest a three-pronged approach:

- First, IRBs should have a basic understanding of what is involved. To this end, we recommend that IRB members read an overview and a relatively short “primer” on the subject.
- If IRB members are not confident in their ability to use those concepts to evaluate a protocol, that should trigger the request for expert advice. IRBs should identify and consult experts in this area (e.g., statisticians, biostatisticians, demographers, sociologists, epidemiologists, or health services researchers who are experienced in the use of data restriction techniques) to review what was proposed by researchers.
- As part of the review process, the IRB may wish to employ documentation in the form of a “disclosure checklist” that would guide the researcher and inform IRB members of the steps taken for statistical protection. The use of a checklist, such as CDAC’s “Checklist on Disclosure Potential of Proposed Data Releases,” could help in determining the effect of those procedures on data quality and whether additional expert review is needed. The cited Checklist was developed to foster best practices across a wide range of sharing and data set characteristics. The Checklist is purposely comprehensive and helps identify the implications of particular kinds of variables for reidentification of subjects. Individual IRBs would need to adopt and adapt those parts of the Checklist that serve the needs of the particular kinds of data generated and shared at that institution. When researchers submit their protocol, they should include a list of the variables they will include in the data set that they plan to share.

More recently, the NIH’s National Heart, Lung, and Blood Institute has developed procedures and standards for the release of data to secondary researchers that are similar to but more stringent than those provided for in the standard for Limited Data Sets of the Health Insurance Portability and Accountability Act’s (HIPAA) Privacy Rule. After review by the data recipients’ IRB, data are released under a signed agreement. In addition, the data released are modified according to guidelines for protecting study participant confidentiality.

The IRB is not a disclosure review board. It is not responsible for reviewing either the resulting manuscripts or data sets and documentation after they have been prepared for sharing. However, institutions may wish to establish a body that is capable of reviewing the data that have been archived for sharing to ensure that the requirements of the HIPAA Privacy Rule are met.

Normally, the concern for IRB members should be whether the statistical disclosure methods researchers intend to use will produce data (intended for sharing or publication) that represent “minimal risk” to participants. Techniques are available for disclosure protection that can accomplish this objective. Most of them are quite straightforward and can be implemented by most data managers and/or researchers. However, if a researcher wants to provide unusual detail (e.g., day, month, and year of birth; age at death in days or months) for small areas or special populations, the data need special attention that only an expert can provide. Selection of the appropriate data restriction methods depends in part on the nature of the data, the vulnerabilities of the respondents and the research institution, and the effects of distortion of the data on the subsequent usefulness to secondary analysts.

Restricted Access

Arrangements can be made for controlling the purpose and location of data use, as well as the protection, redisclosure, and final disposition of the data. These arrangements may include supervised use by a guest researcher at the principal researcher’s institution, research data centers/enclaves, or a remote access system; alternatively, data might be used under legally binding “licenses” at the secondary researcher’s institution. A brief description of one of these restricted access methods, access via a research data center or data enclave, follows.

Data Enclave or Research Data Center. Sensitive quantitative data, usually without direct identifiers such as name and address, may be maintained in a secure archive (research data center or enclave). The enclave staff may perform requested analyses for the secondary user, often for a fee. Alternatively, the secondary user may come to the archive and perform the desired analyses on a dedicated computer, with a disclosure review of all output, inspection of material to be removed from...
the site, and physical oversight by the resident staff. Typically, in either situation where the data remain in an enclave, the secondary user submits a research proposal and enters into a formal agreement about the work that is to be done and the kinds of output sought. The application is usually extensive, including personal identification and institutional affiliation, a current resume, dates of proposed use of the enclave, source of funding, a detailed account of why the data are needed, and the parts of the data set that are needed. There may be limits on the types of analysis permitted and on any outside (linkable) data brought in by the secondary user. In some contexts, when the data are highly complex, the secondary user may stay at the site for a long period of time under a fellowship arrangement.

A data enclave may be established at the home institution of the investigator; or, in some cases, in an enclave under the auspices of the funding agency. For example, the U.S. Census Bureau and the National Center for Health Statistics have research data centers.21

Review of Output Based on Data Shared in a Data Enclave. Shared data used under a restricted access agreement typically consists of an electronic file that will be analyzed by the researcher. Such "final research data" (microdata file) are used to generate statistical output (e.g., tables). This output should be reviewed by those having expertise in statistical methods to limit disclosure. As we noted earlier, the research data centers funded by federal statistical agencies review analytic results before a researcher is allowed to take them off-site.22 In such cases, the output rather than the data file is deidentified.

Similarly, the University of Michigan’s Health and Retirement Study requires a disclosure review prior to removing output from its enclave, the Michigan Center on the Demography of Aging Data Enclave.23

Data Sharing Agreements

Data sharing agreements are used to impose appropriate limitations on users. For example, they would include the criteria for data access, stipulate confidentiality standards to ensure data security at the recipient site, and prohibit manipulation of data for purposes of identifying subjects. They typically also state that the recipient may not transfer the data to others, that the data are to be used only for research purposes, and that the proposed research will be reviewed by an IRB. Penalties are typically included for violating the terms of the agreement.24 The consent statement should be consistent with the method of data sharing.

Many examples of data sharing agreements for specific data sets are available on the Internet, e.g., obtaining a restricted use data license with the National Center for Education Statistics and using restricted access data files from the University of Michigan’s Health and Retirement Study.25 There are many data use agreements posted on the Internet specific to the requirement of the HIPAA Privacy Rule; to our knowledge none have been tested in the courts.

Data sharing agreements may be developed by individual researchers in consultation with their institutional research administration. Such agreements are also developed by archives that accept researchers’ documented data and administer the sharing of these data. For example, the Murray Archive stores and administers the sharing of psychological data among which are developmental studies whose data include videotapes of individuals and families. The Murray Archive has a process through which potential users apply for data.26 Depending on the nature of the data sought, an appropriate data sharing agreement is reached with the borrower. Other useful models can be found on the web sites of the research data centers sponsored by the federal statistical agencies.27

Implications for IRBs and Research Administrators

Institutions that anticipate generating data that are to be shared need to consider how they will meet requirements for responsible and legal sharing. How is this done? The simple answer is that the major responsibility for creating an appropriate sharing arrangement falls to investigators. However, as every IRB chair or administrator should know, such activities work best when the IRB is knowledgeable and can offer useful guidance to naive investigators. There are four areas in which guidance and shared understanding are important: costs of sharing, confidentiality measures, informed consent in relation to data sharing, and, in the case of medical data, compliance with the HIPAA Privacy Rule.

Costs. Researchers and research administrators, including IRBs, need to anticipate the costs of data sharing, which may include the cost of data documentation, preparation of restricted data, consultation with those having expertise to assess the risk of reidentification, and appropriate preparation of items to be shared. There is little point in agreeing to share data if one does not
budget for the cost of doing so properly. If data are to be archived at the investigator’s home institution, appropriate space and staffing requirements must be met. Most funders permit these costs to be included in the proposal budget.

- **Confidentiality.** The IRB needs to know about reidentification issues and whether the proposed restricted data or restricted access arrangements will reduce disclosure risk to an acceptable level. If this determination is beyond the expertise of IRB members, the IRB should consult with someone who is qualified to provide advice on this matter, such as a statistician who is knowledgeable about statistical disclosure limitation methods.

- **Informed Consent.** If data sharing plans have been developed responsibly to minimize the possibility that any subjects could be identified or reidentified, then, according to federal human research regulations (the Common Rule), the data are not human subjects data, and subjects’ permission need not be obtained for sharing. Some projects let research participants know that the data will be released in aggregated or deidentified form, even though this is not a legal requirement. The decision to include such a statement might depend on the nature of the project, the likelihood that the subjects will understand the statement, and on the feasibility of adding length to the informed consent statement.

However, if sharing of identifiable data, e.g., videotapes, is anticipated, it is prudent to inform subjects of sharing plans even if restricted access arrangements would preclude irresponsible use or identification of individuals by secondary users.

- **HIPAA Privacy Rule.** If the research involves individually identifiable health data covered by the HIPAA Privacy Rule, the IRB will want to understand the implications of the Privacy Rule for researchers. For example, the Privacy Rule does not restrict the disclosure or sharing of medical data that have been properly deidentified.

While primary responsibility rests with investigators, who in turn can obtain much relevant assistance from their funding agency via their program officer, the IRB and others in the institution’s research administration still have considerable independent responsibility. Most funding agencies will be sensitive to the adequacy of the proposed data sharing plan. However, the institution’s research administration nevertheless has a role in ensuring that proposals for projects that will involve data sharing provide a concise description of how the data will be documented and prepared for sharing, how risks of disclosure will be identified, and what means will be employed to restrict data or access, as appropriate.

Depending on the nature of the research and of the anticipated data, the identification of disclosure risks and selection of appropriate restricted data or restricted access methods typically require special, though not extraordinary, expertise. Those most likely to have such expertise or to be able to develop that expertise efficiently are statisticians or persons with considerable knowledge of statistics and research design (including some epidemiologists, sociologists, and health services researchers). For expertise in data linkage techniques that can be used in reidentification, an information specialist or computer scientist might need to be contacted. The IRB and investigators may need to collaboratively develop a request of their research administration to provide these needed resources. Some institutions may wish to provide the necessary training to a small group of statisticians within the institution, and possibly others who have considerable competency in the area of quantitative research design. This group of experts could comprise a Disclosure Review Board and could adapt the CDAC’s Checklist for its own use.

How can investigators, IRBs, and other research administrators gain the needed knowledge and expertise required to understand and oversee the work of a Disclosure Review Board or an expert who consults with the IRB on matters of preventing disclosure without outside help? Fortunately, relevant information exists on the Internet. The American Statistical Association’s Committee on Privacy and Confidentiality has created a comprehensive Internet resource that offers most of the information one would need to develop and maintain expertise in methods of assuring the confidentiality of human research data that are to be shared. In addition, the Confidentiality and Data Access Committee offers special training courses in these subjects, some of which are available on video.

As mentioned earlier, the Checklist is an example of best practices for a wide variety of sharing activities. It was developed under conditions that may not be strictly applicable to every institution. However, portions of it may usefully be adapted to the needs and circumstances of institutions wishing to appoint an individual or a committee responsible for reviewing data sharing plans or data that have been prepared for actual release. Alternatively, the Inter-university Consortium for Political and Social Research is a publicly accessible archive which will deidentify data at a cost to the data
Acknowledgments

The authors want to thank all individuals who reviewed drafts of their paper, including Janet Chiancone, May Chu, Patrick Clark, Donna Eden, Peter Joffis, Michael Nolte, and Deborah Tress.

Virginia A. de Wolf, PhD, is a United States Federal Statistician (retired); Joan E. Sieber, PhD, is Professor of Psychology, Emerita, at California State University East Bay, Hayward, CA; Philip M. Steel, MS, is Disclosure Avoidance Staff Member at the United States Census Bureau, Washington, DC; and Alvan O. Zarate, PhD, is Confidentiality Officer at the National Center for Health Statistics, Hyattsville, MD.

References

7. One method of masking outliers is to replace large values with an amount related to the distribution of those large values. For example, in a survey several individuals reported incomes of $2,000,000 or more. After reviewing the distribution of incomes, the researcher decided to consider all incomes greater than $2,250,000 as "outliers" and replaced these values with the mean of all incomes greater than $2,250,000. This method is called top-coding. See ref. 2, p. 66.
8. This involves the addition of, or multiplication by, a random number with a given distribution to data. See ref. 2, pp. 66-67.
9. A small percentage of the records are matched with other records on a set of predetermined variables. For pairs of records values of variables not used to match the records are swapped. See ref. 2, p. 67.
10. Values of continuous variables are sorted, and values that are close in rank are swapped between pairs of records. See ref. 2, p. 67.
11. It involves aggregating values across small sets of respondents for certain variables and then replacing a reported value with the mean of the group. See ref. 2, p. 67.
12. See refs. 3 and 4.
13. See ref. 6, Duncan 2003.
18. In ref. 16, see 45 CFR 164.512(a)(1)(i) for uses and disclosures for research purposes.
22. See the U.S. Census Bureau's research proposal guidelines in ref. 19. In the subsection entitled "The Proposal Process," the paragraph on "Risk of Disclosure" begins by stating that "Output from all research projects must undergo and pass disclosure review."
24. For instance, the National Center for Education Statistics may immediately revoke the license and, if the violation warrants, pursue legal charges with a fine up to $500,000 and even seek imprisonment. http://nces.ed.gov/scpap/rudmanr.asp.
25. See ref. 20.
27. See ref. 21.
29. See ref. 14.
Trials and Errors: Barriers to Oversight of Research Conducted under the Emergency Research Consent Waiver

Despite the Nuremberg Code's assertion that "the voluntary consent of the human subject is absolutely essential," federal human research regulations permit both consent from legally authorized representatives (LARs) for incapacitated subjects, and waiver or alteration of informed consent for certain minimal risk research.¹ In 1996, the regulations were amended to permit a limited category of research bearing more than minimal risk to go forward without informed consent from either incapacitated subjects or their LARs. Known as the "emergency research" (ER) waiver rule, the regulation was codified in Food and Drug Administration (FDA) regulations² and adopted by the Department of Health and Human Services (DHHS).³

Though controversial and infrequently employed, the ER waiver rule is valued because it facilitates important research in settings where new, well-validated treatment options are needed and circumstances preclude obtaining informed consent from an incapacitated individual's LAR. The first clinical trial conducted under the ER waiver rule was a widely publicized study of an oxygen-carrying blood substitute: Baxter Laboratories' HemAssist.⁴ Another trial conducted under the rule involved placing automated defibrillators in public venues and tracking the outcome of their use from experimental and control sites.⁵ Individuals felled by cardiac arrest formerly had to wait for emergency medical personnel to arrive before receiving needed defibrillation. Because of the study, automated defibrillators are now common in airports and other public places.

The ER waiver rule permits Institutional Review Boards (IRBs) to waive the requirement for informed consent from an incapacitated individual's LAR when certain conditions are met.⁶ These include familiar protections such as evidence from prior research supporting the experimental intervention's potential to benefit patient subjects and the establishment of an independent data monitoring committee. Additional conditions are specific to a narrow application of the waiver: patient subjects are in a life-threatening situation that necessitates intervention; obtaining informed consent from an LAR is not feasible within the time period necessary to initiate the experimental intervention (i.e., the therapeutic window); and available treatments are unproven or unsatisfactory. Finally, the conditions require researchers to 1) consult with representatives of the communities in which the research will be carried out and from which subjects will be drawn and 2) publicly disclose to those communities the research plan and its potential risks and benefits.

During the community consultation process, people can register their views about the proposed study. IRBs are expected to consider community views when reviewing a request for a waiver of consent under the ER waiver rule. After obtaining IRB approval for the study, researchers must disclose to the public that incapacitated individuals can be enrolled without consent from an LAR.⁷

Some time ago, we became concerned about the applicability of the ER waiver rule to the ongoing trial of PolyHeme, Northfield Laboratories' hemoglobin-based oxygen-carrying resuscitative fluid. If it were to merit FDA approval, the product could save the lives of trauma victims initially being treated in an out-of-hospital setting. Because blood transfusion is ordinarily unavailable in the field, trauma patients often succumb to hemorrhagic shock before reaching the hospital.

The Trial and Its Error

The PolyHeme trial has two stages: an ambulance stage and an in-hospital stage. Trauma patients in hemorrhagic shock are enrolled in the trial by emergency medical technicians at the scene of accident or injury. Patient subjects are randomized to receive either saline solution (the standard but admittedly unsatisfactory treatment) or PolyHeme. They are then
transported to the hospital, where those who received saline continue to receive standard treatment, now including blood as needed. Those in the experimental group continue to receive up to six units of PolyHeme for up to 12 hours—instead of blood.8

Because blood is available at the hospital, and is an effective (albeit imperfect) standard treatment for hemorrhagic shock, denying half of the patient subjects blood for up to 12 hours does not, in our view, meet the criteria for the ER waiver rule, which requires that available treatments be “unproven or unsatisfactory.” In the hospital setting, blood is neither. An in-hospital trial comparing PolyHeme with blood could be valuable and legitimate, but consent from the patient subject or an LAR should be required.9

The research had been misleadingly described as an “ambulance trial.”10 When we finally appreciated the in-hospital problem, we corresponded with an official from the trial’s sponsor, Northfield Laboratories. The sponsor’s arguments for in-hospital use of PolyHeme were premised on the adverse effects of blood. Following a failed effort to persuade the sponsor’s representatives that the study design did not meet the ER waiver rule, we contacted the FDA. The FDA acknowledged our communications without comment. As we pressed on, we discovered three barriers to effective oversight of research conducted under the ER waiver rule.

Barrier #1: Proprietary Protocols

When we asked to see the protocol, we were told that its disclosure was limited to IRBs reviewing the study or researchers carrying it out, and then only pursuant to a confidentiality agreement. Although industry sponsors of research have legitimate interests in protecting trade secrets and confidential commercial information, little systematic attention has been given to the effects of this degree of information control in clinical research. When a commercial sponsor labels its research data as proprietary, a conflict arises between protecting competitive advantage and protecting subjects (and perhaps future patients as well). In research requiring community consultation and public disclosure, when an entire protocol is considered proprietary, the sponsor’s interest in protecting its competitive advantage also conflicts with the community’s right to transparency. It seems to us that if community consultation is to be adequate and effective, the community’s need for information must outweigh the commercial interests of a sponsor. Commercial secrecy thus appears directly at odds with the free and full discussion required by the ER waiver rule. The protocol should be available for review. Despite repeated requests, we have yet to see the protocol for the PolyHeme trial, or even any version of the consent form.11

Barrier #2: Derailing IRB Disapprovals

If an IRB determines that it cannot approve proposed research—because it does not meet the criteria for the ER waiver rule or “because of other relevant ethical concerns”—the IRB must document and report its disapproval promptly to the sponsor and local investigator. The sponsor then must promptly report the IRB determination to the FDA, to the sponsor’s other investigators, and to other IRBs who have considered or are considering the study or substantially equivalent research.12

In communications with several members of IRBs that reviewed the proposed PolyHeme trial, we uncovered two strategies for sidestepping these reporting requirements. In both instances, the concerns IRB members had about the trial were essentially identical to the problem that troubled us: its in-hospital portion.

In one case, the principal investigator (PI) had been alerted in advance that some on the IRB had expressed reservations about the trial. Before the full IRB convened to review the proposed study, the application for review was withdrawn. The IRB neither completed its review of the proposed study nor reported a failure to approve. In a second case, the IRB notified the PI that there were problems with the study needing correction. The application for review was returned to the investigator with a request to amend and resubmit it. The IRB never received an amended version of the application, and no negative report was sent to the sponsor.

It could be argued that these examples are consistent with a narrow interpretation of “cannot approve” in the ER waiver rule because neither IRB made a final determination about the research. From our perspective, however, the requirement that the IRB’s findings be disseminated promptly appears intended to promote communication and learning among IRBs and investigators. We worry that IRBs and sponsors can too readily avoid reporting problems with proposed studies to those needing to be informed. If serious reservations about a study identified during IRB review were generally buried in this way, the national system of research oversight would be compromised.
Barrier #3: The Special Protocol Assessment

The PolyHeme study is being conducted under an FDA-granted Special Protocol Assessment (SPA). The 1997 FDA Modernization Act contains provisions designed to streamline the approval process for drugs and biologics, including the making of agreements between the FDA and sponsors about the amount and nature of the evidence required to establish safety and effectiveness and rapid assessment of protocols to determine whether they can produce adequate evidence. In May 2002, the FDA issued a guidance on SPAs. When granted, an SPA locks the FDA and the sponsor into an agreed-upon study design. The FDA can reconsider and order changes only if one of four conditions applies: 1) there is mutual written agreement to alter the trial; 2) there has been a subsequent identification of “a substantial scientific issue essential to determining the safety or effectiveness of the drug”; 3) the sponsor fails to follow the agreed-upon protocol; or 4) “the relevant data, assumptions, or information provided by the sponsor in a request for special protocol assessment change are found to be false statements or misstatements or are found to omit relevant facts.” The FDA can only grant an SPA before subject screening or enrollment begins.

There is a tension between community consultation in trials under the ER waiver rule and the SPA’s timing. The study can begin only after a sponsor has first received written permission from the FDA and, later, IRB approval. But IRBs can approve the protocol only after community consultation. If, as we believe, one purpose of community consultation is to uncover correctable problems, the prospect of having to reapply for an SPA discourages the sponsor from changing the protocol when errors are found. One would expect a “take it or leave it” approach to community consultation if a study design could not be altered without costly delay.

More important, the SPA appears to bar the FDA from taking corrective action. The identification of ethical concerns is missing from the list of four conditions warranting FDA reconsideration. Even if the FDA agreed that our ethical critique of the PolyHeme trial were sound, it is not clear it could require alteration of the study on that basis, having previously approved the study design under an SPA. We do not know how often sponsors seek SPAs for clinical trials, but can well understand the desire to clarify in advance what design and data will suffice for FDA approval. We are not the first to recognize that SPAs can constrain IRB review. We suspect, however, that the PolyHeme trial is the first to uncover conflict between the requirements of an SPA and those of the ER waiver rule.

Discussion and Recommendations

In attempting to learn more about the PolyHeme trial, we found heretofore-unsuspected conflicts, tensions, and gaps in the oversight of research conducted under the ER waiver rule. Taken together, these appear to diminish responsiveness to ethical concerns arising in this unusual category of clinical trial. The proprietary sequestration of essential documents; the apparent sidestepping of the requirement to report IRB failures to approve; and the granting of SPAs that constrain community consultation and cripple FDA reconsideration: all three suggest a dysfunctional system.

The PolyHeme trial suggests that in an increasingly competitive atmosphere, the still-unfamiliar requirements of the ER waiver rule can too easily be interpreted away. We argue that when requirements of the ER waiver rule appear to conflict with other FDA provisions and procedures, more attention must be given to ensuring that the ethical integrity of the ER waiver rule is maintained. We recommend that, at the very least, IRBs reviewing such research should determine whether it involves a confidentiality agreement or an SPA, and disapprove the research unless those provisions are altered to ensure adequate and effective community consultation and public disclosure.

In addition, DHHS’s version of the ER waiver rule contains language absent in the FDAs: “A periodic review of the implementation by IRBs of this Section 101(i) waiver will be conducted by [the Office for Human Research Protections (OHRP)], to determine the adequacy of the waiver in meeting its intended need or if adjustments to the waiver might be necessary and appropriate.” Although the FDA has exclusive jurisdiction over waived-consent trials conducted under FDA regulations, such as the PolyHeme trial, the OHRP appears to have the authority to conduct such a periodic review. We believe that a review of these broader issues, collaboratively undertaken by the OHRP and the FDA, is now necessary to ensure open discussion of the future of the ER waiver rule.

Properly conducted, waived-consent research can augment the capabilities of emergency medicine. It would be tragic if avoidable failures and conflicts in oversight compromised the promise of these trials.
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References


6. See ref. 2.


10. See ref. 8.

11. Every study site must have an IRB-approved consent form available, in case informed consent can be obtained from a subject or an LAR. See ref. 2; Japsen B. Paper barred from using data: Northfield Labs sues on blood substitute. Chicago Tribune, January 7, 2006. http://www.chicagotribune.com/business/chi-0601070106jan07,1,5904816.story?track=1&cset=true.

12. See ref. 2.


15. “Community consultation refers to ensuring that the community is (are) involved in the IRB’s decision-making process. As such, the IRB needs to provide an opportunity for the community to discuss the proposed clinical investigation and its risks and potential benefits, and to provide feedback to the IRB. The IRB should consider this community consultation when reviewing the protocol.” Food and Drug Administration. Draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research. March 30, 2000, p. 6. http://www.fda.gov/ora/compliance_ref/bimo/emfinal.pdf.


17. See ref. 3.
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