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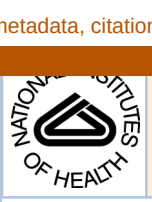

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APPLYING RESEARCH ETHICS GUIDELINES: THE VIEW FROM A SUB-SAHARAN RESEARCH ETHICS COMMITTEE

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Abstract

Considerable variation has been demonstrated in applying regulations across research ethics committees (RECs) in the U.S., U.K., and European nations. With the rise of international research collaborations, RECs in developing countries apply a variety of international regulations. We conducted a qualitative descriptive pilot study with members of the national REC in Malawi to determine criteria they use to review research, and their views on international collaborations. Qualitative content analysis demonstrated that international guidelines are interpreted in light of local African conditions such that emphasis is placed on examining benefit to the community and ensuring the informed consent process translates concepts in locally-meaningful ways. Members suggest that RECs often must comply with regulations that do not fit local conditions. Recommendations are provided for improving such international collaborations.

Keywords

Research ethics; ethics review; REC; Africa

The mandate of research ethics committees (RECs) is to ensure that human subjects research is conducted in ways that minimize risk of harm to subjects and balance risks with anticipated benefits. Studies of such committees in the United States (U.S.), the United Kingdom (U.K.), and Europe have documented variation in how regulations are applied and in consistency of review across different institutions (Bell, Whiton, & Connelly, 1998; Department of Health and Human Services [DHHS], 1998; Alberti, 1995; Alberti, 2000; McWilliams et al., 2003; Silverman, Hull, & Sugarman, 2001; Cooper & McKee, 2001).With the rise of international research collaborations, RECs in developing countries often apply U.S., U.K., European, or other international regulations. These RECs face additional challenges posed by limited resources, poorly defined lines of authority between

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RECs and external parties including investigators and other RECs, and the proliferation of new types and increasing numbers of research protocols.

At the same time, clinical research conducted in developing countries has also produced a number of controversies related to justice, standard of care, and sustainability. These have been raised in commentaries from developed (e.g., Angell, 1988) and developing nations (e.g., Del Rio, 1998; Bhutta, 2002; Benatar, 2000) and have been influential in the revision of international guidelines. For example, the Declaration of Helsinki revision in 2000 and Council for International Organizations of Medical Sciences (CIOMS) revision in 2002 were aimed in large part to address issues such as placebo-controlled trials and post-study access in developing regions. Not all revisions harmonized, however, as in the case with revisions to the Declaration that rule out research with healthy children or those incapable of giving consent, creating contradictions with CIOMS and U.S. guidelines. While dilemmas in international research ethics have been raised in the bioethics literatures (e.g., Macklin, 1999; National Bioethics Advisory Commission, 2001; Benatar, 2004), there have been few reports on the views of local RECs. For this reason, we initiated a qualitative, descriptive pilot study of members of one such REC in Malawi, in 2004, in order to understand their perspectives on how well international collaborations work and what they look for when they review such protocols.

Methods

In June 2004, in-depth interviews were conducted with 11 of 14 members of the Malawi National Health Sciences Research Committee (NHSRC). Three members were either out of the country or could not be reached for the interviews. The NHSRC is the national REC in Malawi associated with the Ministry of Health; a second REC was established at the College of Medicine in the late 1990s and shares many members with the NHSRC.

The purpose of the interviews was to determine the criteria used by the committee to review research protocols, to better understand the challenges they face, to gain knowledge of their perceptions of international collaborations, and to explore how to build successful relationships with research ethics committees in the United States and elsewhere. Topics included specific questions about the review process, including how they assessed informed consent, risk, benefit, and vulnerable populations; the role of the ethics committee and relationships with other committees; potential influences on independent review; and overall assessments and training needs. A separate questionnaire was used with the REC Chair.

Interviews were conducted by an American medical student in English and each lasted between 1 and 1.5 hours. Each interview was audio-taped and transcribed word-for-word. Because of the pilot nature of this research, we chose to use an in-depth interviewing approach, with an interview guide that did not require questions be asked verbatim or in identical order in each interview. Qualitative content analysis was used to analyze the data. Three authors reviewed all transcripts to understand each REC member’s individual perspective on the interview topics, and the lead author identified broad deductive codes based on study objectives. Working independently, each transcript was coded by two authors and then reviewed in a group to identify and discuss the main themes that emerged within each broad code. Quotes were identified within each code as representative of the perspectives of several REC members. Results presented here are a summary of the main areas discussed within these codes and were confirmed by follow-up discussions with the REC members. The research was approved by the Malawi NHSRC and the Institutional Review Board at the University of North Carolina at Chapel Hill. All participants gave their verbal informed consent.

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Results

THE HISTORY, DEMOGRAPHICS, AND REVIEW ACTIVITIES OF THE REC

Established in 1988, this REC, referred to as the National Health Science Research Committee, falls under the supervision of the National Research Council of Malawi but is housed in the Ministry of Health. At the time of the interviews, the REC had 14 regular and four alternate members, including four medical doctors, four with other doctorate degrees, five with masters degrees, and five with bachelor degrees. Four members were women; non-scientific members included an ethicist and a sociologist. The REC met every three months (currently every two months) and reviewed 40–50 new protocols annually. Of these, 10 to 15 each year were judged by the Chair to involve no more than minimal risk and given expedited review.

Approximately half of the protocols reviewed by the REC were international collaborations. Most originated in the U.S. or U.K., were on HIV/AIDS or malaria, were directly funded by the National Institutes of Health, U.K. universities, Wellcome Trust, or the Global Fund to Fight AIDS, Tuberculosis, and Malaria. The REC relied upon ethical guidelines put forth by the WHO (World Health Organization [WHO], 2000), although they also consulted guidelines from the U.S. DHHS, CIOMS, and the Declaration of Helsinki.

INFORMED CONSENT

REC members agreed with the principle of voluntary, informed consent; however, they expressed doubt about the effectiveness of the current informed consent process used by researchers. As summarized by one REC member [*Participant #5*]: “We agree with the principle of informed consent … and that people have to understand, but in fact this is not happening. So the question is should we stick to the things that are not working? We should not have lower standards, but your principles are not working on the ground.” Members’ concerns focused primarily on the belief that potential study participants typically do not fully understand information presented to them during the consent process. Inadequate time given to participants to explain the research was identified as a cause of limited understanding. An REC member explained: “The problem is that very little [time] is spent explaining to people what the study is all about. … More time must be spent for the subjects to know … why it is being conducted, what you want to achieve at the end of the day, and then we need to make sure the subjects understand what the study is all about.” [*Participant #7*] Members believed, however, that participants *would* be able to understand consent information if adequate time for discussion was provided. One member said: “If you give it time according to the literacy level of the subject, then I think it is possible [for the respondent to understand consent information]” [*Participant #2*].

REC members also stressed that participants’ low literacy and difficulty with understanding long scientific explanations must be addressed. Consent forms must be written in language “using the simplest terms possible so that the subjects can understand.” [*Participant #2*] They emphasized not only the importance of *translating* the consent forms into the local language, but the need for *transferring the meaning* of concepts: “The consent form has to be translated into the local language so that people can understand … and it is not just a question of translation, but it has to carry the meaning in the original version.” [*Participant #8*]

Another reason cited for limited understanding was the length of the consent forms. Several REC members questioned why American RECs approved such long consent forms when it is clear they are difficult for participants to understand, suggesting that the consent forms serve as legal documents to protect researchers: “Researchers are not going to read a 30-page consent form to the subject … You have made it a legal document and nothing more.”

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[*Participant #6*] Members stressed that forms must be short and precise. Moreover, as stated by one REC member: "A long informed consent is defeating the whole objective … Too much information is not understandable." [*Participant #5*] Another member said: "We believe that the longer the consent form, the possibility of the subject to lose concentration [increases.]" [*Participant #8*]

Consistent with findings from other studies (Kass, Sugarman, Faden, Schoch-Spana, & Trust, 1996), REC members noted that some participants agree to participate in research simply because they trust researchers, whom they believe will do their best for them or their child. Thus, the REC looks for statements in consent forms that stress voluntariness. As stated by one REC member: "[Are researchers] *asking* [for participation] versus *demanding* … Are they giving the individual a choice?" [*Participant #2*]

VULNERABLE POPULATIONS

Several observed that autonomy must be understood in the Malawian context, that is, "[in Malawi] you can talk about autonomous communities and autonomous groups, but not autonomous individuals. It doesn't mean that people do not make personal decisions … there is a need for individual autonomy for personal identity, [but] here autonomy is relational." [*Participant #5*] The influence of local leaders over these decision-making processes has moderated in recent years. Village chiefs still must be informed of impending research in their community, but "… people know they have rights now. The chief might say yes, [yet one should not] take it for granted that everybody shall say yes." [*Participant #7*]

REC members perceived study subjects in the U.S. and U.K. to be more independent in their decision-making, yet one member observed: "I don't know how truly autonomous a poor person is in America. Autonomy suggests that you have alternatives … A lot of the difference between the West and Africa does not have to do with what we're discussing [autonomy]. It has to do with being rich and poor." [*Participant #6*] Poverty was cited by almost everyone as a sign of vulnerability, and "… virtually every person enrolled in studies in Malawi is poor." [*Participant #6*] As well, limited education was mentioned, and a few respondents identified gender as a source of vulnerability because of its link to poverty and low literacy.

RISKS

With so many studies of HIV and other infectious diseases, almost all REC members mentioned stigma as a primary risk of research participation. For example: "When [study staff go to a participant's house] to draw blood to test for HIV, what will the community talk about? They will say this person has HIV … so we look at such risks." [*Participant #4*] As a result, REC members explained that they spend significant time examining risks beyond the potential physical risks and evaluate the potential for research procedures to identify and stigmatize participants. As explained by one member: "We look at social risks such as risks to privacy and confidentiality. Social risk can become a physical risk, for example, if a wife participates in HIV/AIDS research and is identified as having HIV, she could be harmed by her husband." [*Participant #5*] Another member [*Participant #6*] discussed the social and ethical implications of a vaccine trial, such that outside the study setting, participants may not be able to differentiate new infection from vaccine-related seropositivity. In addition, this member explained: "[the implications of testing HIV positive] was discussed at length when reviewing vaccine protocols … We were more concerned about social-psychological issues almost than we were about the physical risks." REC members also understood that minimizing stigma was also "clearly in the researcher's best interest because if you stigmatize people, they won't come or they won't return." [*Participant #6*]

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BENEFITS

When assessing benefit, one member summarized the committee's views by stating: "… first we look at the benefits to the community." [*Participant #8*] Every REC member emphasized that they examine the benefit to the community in particular and focus less on individual benefits, and in the review process they look "to see if the investigator has put any effort to inform the subject what the benefits are for the individual *and* for the society." [*Participant #1*] Examples of community benefits included addressing underlying health problems, bringing in new medications, or creating infrastructure, noting that the committee pays attention to whether projects will 'build capacity.' This concern was linked specifically to the experiences with HIV research, which "brought [the issue] to the forefront. In developing countries, where you're left high and dry once the study finishes, it's always an ethical dilemma." [*Participant #6*]

It was important to clarify that research might not benefit individual participants. One member explained: "… I think it's too narrow of a view to suppose that every research project undertaken will be of benefit to the individual. I think there is a real view that the community needs to feel happy that even though they don't benefit now, they may benefit in the future. It's important to make people aware of that. If we insisted on those particular benefits [to the individual], you would never get any basic research done at all." [*Participant #6*] Another member articulated a hierarchy of benefits: "First of all we look at the benefits to the community, and not to the individuals. And also we look at how the study is going to benefit the institution doing the study … Finally, we can look at the benefits to the individuals." [*Participant #8*] While members recognized that community benefit, such as construction of a hospital, can also benefit the individual, one member said: "… usually we discourage [discussing] individual benefits because it is like coercing people into the study." [*Participant #4*]

The Role of REC in International Collaborations: Barrier or Facilitator?—REC members believed that local and international researchers have "mixed views" about their committee and its role. When asked how they believe international investigators perceive their REC, many said they were seen as "police officers," blocking research and delaying scientific progress. They feel pressure from such statements by international collaborators as, "This study was already approved by our country, why are you taking so long?" and said that investigators who think that they will have "an easy ride … are shocked" [*Participant #5*] when the REC does not automatically approve their studies. One member stated that researchers in Malawi have "more responsibility than in the U.S. to make sure that they maintain the public trust," [*Participant #6*] and several REC members expressed concern about protecting the country's ownership rights to research results. For example, one member said: "The government should be aware of whatever you want to publish or do with the data. After all, you are doing the study to solve problems which are affecting the people in Malawi." [e.g., study data collected in Malawi is property of the Malawi government.] [*Participant #9*]

Conversely, members felt that many international investigators appreciate the REC's contributions to the ethical conduct of research. This can take the form of logistical help in study design and execution, but is most commonly described as making the research "culturally feasible." This role of culture broker was identified in several interviews. It was suggested that local investigators are a key component since, "if you don't have local investigators, then you don't have insight into what is culturally acceptable." [*Participant #6*] As an example, several members mentioned misunderstandings when researchers proposed to draw blood, causing fear that they would sell it or "play magic" with it. In

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response, the REC strongly counsels researchers to engage in community education prior to recruitment.

The interviews also revealed a tension between balancing the promotion of the research and the protection of the study participants. As described by one member: "When we review protocols, we make sure that human subjects are protected; that is number one. We make sure that research is done accordingly and we make sure that human subjects are protected." [*Participant #10*] On the other hand, one member called attention to difficulties experienced by researchers when they submit protocols for review: "I feel … human [subjects] are protected by giving the right information … I am afraid [however] that we can see the researcher being [disadvantaged], in fact … because we concentrate very much on the research participant, we have seen that [RECs] are very strict on simple things to the point of actually hindering research." [*Participant #5*]

Lastly, members were concerned that no formal or informal mechanisms for communication existed between international RECs and the Malawi REC. Members expect international collaborators submitting protocols to have them reviewed by their own REC first, but they also believe that the final decision is theirs: "Clearly people are influenced by what other RECs have said, but the final say is with us." [*Participant #6*]

Discussion

A qualitative descriptive study with members of only one REC has limited generalizability, particularly in light of documented variation in history, demographic characteristics, and review procedures among African RECs (Kass et al, 2007; Kirigia, J.M., Wambebe, C., & Baba-Mousa, A., 2005; see also Sugarman, J., Popkin, B., Fortney, J, & Rivera, R., 2001). In their report of 12 African RECs, ranging from several that were established recently to one founded in 1967, Kass and colleagues (2007) concluded that committees become more stable, equipped, and trained over time. In comparison to the RECs described in their report, the Malawi NHSRC is average in terms of number of members, protocols reviewed, proportion of international vs. domestic protocols, and identification of strengths and challenges. Descriptions of difficulties with informed consent forms and requirements from external sponsors or investigators are similar to those reported by Sugarman and colleagues (2001) based on data gathered during focused site visits in eight countries.

In this pilot study, we found that various international research ethics guidelines are interpreted by this REC in light of local African conditions, such that emphasis is placed on examining benefit to the community and ensuring that the informed consent process translates concepts in locally meaningful ways. International investigators are advised about how to proceed in culturally appropriate ways and to collaborate actively with local investigators. While not surprising, these findings provide empirical evidence that normative guidance at the national and international level is being implemented by an REC in this African setting. In addition, the interviews did not reveal close attention to a particular international guideline or to differentiating between U.S., U.K., and European guidelines, but rather, as is typical in the U.S. as well, the REC members discussed how they applied general principles rather than specific regulations.

This REC demonstrated considerable sophistication as members review protocols and balance competing interests. While protection of human research subjects is defined in the regulations as their primary objective, RECs take various stances vis-à-vis the research enterprise, some collaborative, some more adversarial. In this way, they resemble RECs in the West (Nelson, 2006b). However, differences were observed with respect to how "benefits" are defined and to the REC role as culture broker vis-à-vis external investigators.

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The REC members' greatest concern is the inadequacy of a legalistic consent process that is not responsive to the needs of local study participants. Echoed by Bhutta (2004), the process of obtaining informed consent for research in developing countries is often unclear, and focuses on written documentation and emphasis on literal translations of consent forms. The complexity and length of consent forms, combined with limited time for detailed discussions with participants, undermine participants' understanding in all countries (Flory & Emanuel, 2004), but perhaps even more so in settings like Malawi (Karim, 1998).

The most striking difference between reviews by this REC and by RECs in developed countries is the priority given to evaluating research in terms of community benefits. This may reflect the communal nature of society; and it may also reflect concern about economic and scientific exploitation that has determined the worldview of many in Africa. Research is judged on standards of "fair benefits," including benefits to participants and populations both during and after research (Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, 2004). These standards are different from those used in the U.S. (Churchill et al., 2003), although a number of international research ethics codes and guidelines have been revised to accommodate demands for social justice in research (CIOMS, 2002).

A corollary to the focus on societal benefit is the different attitude expressed by REC members regarding voluntary and autonomous decision-making. A number of authors have written about the limitations on individual autonomy in Africa, and the potential consequences for subjects' voluntariness (Ijsselmuiden & Faden, 1992; Kasenene, 1994; Dawson & Kass, 2005), although the relative balance of consent (communal, family, and individual) needed in traditional societies is still uncertain (Bhutta, 2004).

Best Practices

Despite limited generalizability, many observations and concerns raised in our interviews resonate with reports from other countries where RECs face similar role tensions (Amdur & Banker, 2005), and increasing pressures and conflicts in competitive, commercialised research environments (Hunter, 2005; Nelson, 2006a; Nelson, 2006b; Campbell et al., 2006). In light of such pressures, some have suggested strengthening local and regional regulatory frameworks and legislation (Chima, S.C., 2007).

To improve the consent process, REC members recommended that investigators spend more time explaining the study to potential study participants. This approach has been described in a review of interventions (Agre et al., 2003) as possibly the most effective method to improve participants' understanding of informed consent. Furthermore, consent forms must be shorter and the meanings of the concepts must be maintained after translation into the local language. A few interventions in resource-poor countries have been successful, including dividing the consent process over several sessions (Fitzgerald, Marotte, Verdier, Johnson, & Pape, 2002) and using a context-specific informed consent approach that includes local explanations and analogies (Corneli et al., 2007; Corneli, 2003). A conceptual framework for improving participants' understanding has also been proposed (Woodsong & Karim, 2005). The need to assure subjects' informed consent is even more urgent in light of the finding that REC members consider stigmatization from association with an HIV/AIDS trial to be so pervasive (Goldin, 1994).

International investigators who plan to conduct research in sub-Saharan Africa—and the RECs at their home institutions—should be aware of *the values of community benefit and relational autonomy* that are part of this REC's framework of human subjects review. They should also be aware of the potentially critical flaws in their consent forms and processes

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that seriously undermine participants' understanding. Changes can and should be made to improve these aspects of international research.

Research Agenda

As identified here, an important next step is to determine mechanisms to improve communications and understanding between RECs in the U.S., U.K., and Europe, and those in developing countries. Additional qualitative research can be carried out with several RECs to determine the best mechanisms to accomplish these goals. Suggested mechanisms identified through such research for improving communication could then be put into practice during a trial period with paired RECs, followed by a formal evaluation to determine effective communication strategies.

Educational Implications

Often the best educational approach is bi-directional exchange. Members of RECs from the West should visit members from developing country RECs to observe their meetings, and gain a better understanding of the local research environment by visiting research facilities and communities. Likewise, members of RECs from developing countries should visit those in the U.S., U.K., or Europe, to become more familiar with how RECs in the West review protocols. Of note, to follow-up the research described here, an author on this manuscript travelled to Malawi and observed an REC meeting, reviewed various local guidelines and operating procedures, informally discussed with REC members their perceived training needs, and together with the Chair of the REC made recommendations for the next steps pertaining to training/continuing education. The Chair of the Malawi REC and a member of the National Research Council then traveled to the U.S., and spent a week observing several RECs in North Carolina and had discussions with University faculty and REC personnel. In addition, three authors on this manuscript provided a three-day ethics training in Malawi for this REC as well as the other Malawi REC. These ongoing interactions have built a level of trust and mutual respect that now support a cooperative review arrangement between the national Malawi REC and our university-based REC in the U.S., providing for reliance on one REC for some aspects of review and reducing duplication of effort. This type of collaboration is increasingly encouraged among U.S. RECs., and is a positive reflection of capacity building and bi-directional education.

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