Title: Ethical Issues in Multicenter Studies

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ETHICAL ISSUES IN MULTICENTER STUDIES

Introduction

Multicenter studies are advantageous for various reasons. Because multicenter studies are conducted at multiple sites, the external validity and, consequently, the generalizability of the findings may be enhanced (Weinberger et al., 2001). Multicenter studies also enhance our ability to investigate diseases or exposures of interest that are of low incidence because they permit enrollment of a larger number of study participants than could be achieved through reliance on one site alone. This increases the likelihood of a sample size that is sufficiently large to assure statistical power. Too, multicenter studies permit enrollment to occur at a faster rate, potentially reducing the costs and logistical difficulties that may be associated with a lengthier recruitment period.

However, multicenter studies also give rise to numerous ethical challenges because they are often conducted across diverse locales, cultures, and political boundaries. The operationalization of informed consent may be particularly difficult, due to varying definitions of autonomy and difficulties associated with reliance on interpreters. Additional issues may be confronted due to differing applications of the concept of vulnerability across jurisdictions, resulting in differing standards for the protection of the vulnerable persons; varying confidentiality protections across sites due to differences in legal provisions that prevail at each site; and inconsistencies in the demands of the various local ethics review committees at the participating sites. Each of these topics is discussed in greater depth below.

Informed Consent

The informed consent of each individual is a prerequisite to their enrollment in research. This requirement derives from the principle of respect for persons, first enunciated in the Nuremberg Code. The consent must reflect the presence of four elements: adequate information, understanding of that information, the capacity to consent, and the voluntary nature of that consent. Accordingly, the information must be communicated in a manner and language that are appropriate to the prospective participant.

Multicenter studies conducted across different cultures and language groups may be difficult because the prospective participants may speak a language that is different from that of the investigative team, or their ability to communicate in the language of the investigators may be limited. These problems may be ameliorated, to an extent, through the use of interpreters, who the investigators may rely on both to communicate the information related to participation and to obtain consent to participate. However, difficulties may continue to exist due to the inability to translate equivalent expressions from one language to another, the omission or erroneous substitution of terms that may result from attempts to paraphrase material, and variations in the prospective participants' understanding of terms used by the interpreters.

The voluntary nature of the consent that is obtained may be questionable in situations in which there exists a differential in the social status and educational level between the interpreter and the prospective participants from whom he/she is to obtain

consent (Marshall, 1992). Individuals of lower social standing or education may be less likely to ask questions of an interpreter who is seen as more powerful.

The concept of autonomy may differ across locales, rendering it more difficult to decide who must be involved in the informed consent process and whose consent to participate must be sought. Depending upon the sites at which the study is to be conducted, the investigator may be required to obtain the consent of local leaders or family elder in addition to that of the individual. Barry (1988: 1083) noted in his discussion of AIDS research in Africa that "Personhood is defined by one's tribe, village, or social group." Similarly, Loue and colleagues (1996: 49) observed that, civil law in Uganda provides

> that an eighteen-year-old male living at home has a legal right to make his own decisions. Customary law, however, dictates that the son obtain his father's consent prior to entering any obligation. Women … often refuse to make a decision regarding their own participation or their child's participation absent the consent of their partner.

Accordingly, it is critical that, in designing informed consent processes, investigators be cognizant of and integrate into the informed consent process variations in concepts of personhood and autonomy.

Vulnerable Persons

The principle of respect for persons requires not only that persons who are capable of deliberation about their personal choices be treated with respect for their capacity for self-determination, by requiring that they provide informed consent as a prerequisite to participation in a study, but also that persons with impaired or diminished autonomy be afforded additional protections against potential harm or abuse. These precepts are clearly enunciated in the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Council for International Organizations of Medical Sciences, 2002) and the *International Guidelines for Ethical Review of Epidemiological Studies* (Council for International Organizations of Medical Sciences, 2005).

The concept of vulnerability has been explained as referring to individuals who have "insufficient power, prowess, intelligence, resources, strength or other needed attributes to protect their own interests through negotiations for informed consent" (Levine, 1988: 72). However, jurisdictions may vary in who is considered to fall within this classification and, consequently, the protections required for prospective participants may vary across sites. As an example, U.S. regulations delineate only pregnant women, children, and prisoners as being in need of special protection (45 Code of Federal Regulations Part 46, 2005), whereas Uganda enumerates a significantly greater number of groups in its ethical guidelines for researchers, including pregnant women, children, refugees, prisoners, soldiers on command, and those suffering from mental illness and/or behavioral disorders (Uganda National Council on Science and Technology, 1998). An even greater number of groups are listed in international documents as being potentially vulnerable, including pregnant women, institutionalized persons, children, those with

diminished capacity for understanding, refugees, patients in emergency rooms, homeless persons, and members of some ethnic and racial groups, among others (Council for International Organizations of Medical Sciences, 2002, 2005).

Variations across jurisdictions may require that mechanisms be implemented at some sites for the protection of vulnerable individuals that will not be required at all sites. Investigators may always provide enhanced protection to all participants, regardless of the site at which they are located. However, depending upon the nature of the protection afforded, the autonomy of prospective participants may be compromised. As an example, in jurisdictions that consider all refugees to be vulnerable in the context of research, the investigators may wish--or may be required to--appoint a participant advocate to provide information to the participants and address their concerns. However, it could also be argued that the provision of an advocate serves to disempower the participants themselves and diminish their ability to act autonomously.

Confidentiality Protections

The mechanisms that are potentially available to protect the confidentiality of the data and the privacy of the participants may vary across sites, as a function of differences in protections afforded by local law, available technology, and concepts of privacy and confidentiality. Consequently, the potential risks of participation in a given study may also vary across sites. This may have implications for recruitment and enrollment of participants, as greater levels of confidentiality and privacy may lessen the barriers to participation. Methodologically, it may be impossible to determine the impact of these differences.

As an example, under U.S. regulations, a certificate of confidentiality is potentially available to protect the identity and identifying characteristics of individuals participating in studies in which highly personal and potentially damaging information is gathered. This includes such things as drug and alcohol use and sexual behavior. A certificate of confidentiality protects such data from being accessed by attorneys, courts, and law enforcement officials for use in civil, criminal, and administrative proceedings. However, this mechanism is available to protect only data collected in the U.S.; it does not apply to data collected from sites outside of the U.S. (National Institutes of Health, 2004). Accordingly, a multicenter study which includes sites inside and outside of the U.S. might provide differing levels of protection for the data across the participating sites.

Ethics Review Committees

Numerous studies have reported delays in the initiation of multisite studies due to variations in the requirements of local ethics review committees across participating sites and delays in the processing of reviews. At least one research group concluded that the multiple reviews that are often necessary result in inefficiency, duplication of effort, overemphasis on some monitoring aspects of the process and underemphasis on others, as well as confusion relating to responsibilities for the safety of the participants (Califf et al., 2003).

As an example, Silverman and colleagues (2001) reported considerable variability across 16 local ethics review committees in their review of survey and informed consent forms pertaining to a multicenter trial that compared lower and traditional tidal volume ventilation in patients with acute lung injury. One of the institutional review committees

waived the requirement for informed consent, while five permitted the use of telephone consent and three permitted the enrollment of prisoners into the study. The reading levels of the approved forms ranged from grade 8.2 to grade 13.4, with a mean reading level of 11.6. Thirteen of the approved forms lacked some of the elements of information that are required by U.S. law.

McWilliams and colleagues (2003) similarly encountered considerable variability in interactions with local review committees associated with the 42 sites participating in a multicenter genetic epidemiological study. Among the 31 sites that responded, it was found that 15 of the review committees required at least two informed consent forms and 10 did not require any form of consent from children. Seven of the review committees furnished expedited review, while the remaining 24 required a full review of the protocol.

Burman and colleagues (2003) found in their examination of the reviews afforded by ethics review committees at 25 different sites participating in multicenter study that a median of 46.5 changes were required on each consent form. More surprisingly, the changes mandated by the local review committees often resulted in an increase, rather than a decrease, in the reading level required for comprehension of the informed consent document, potentially reducing the likelihood that participants would be able to understand the form.

In one study of birth weight and child development, 118 of the 145 committees to which investigators applied for approval for the study required completion of different application forms (Middle, Johnson, Petty, Sims, and Macfarlane, 1995). Although almost three-quarters of the committees approved the protocol with no objections, a

number of them expressed reservations relating to confidentiality, the wording of the information sheets, and the questionnaire that was to be utilized in the study.

Hewson, Weston, and Hannah (2002) reported on their experience obtaining approval from local ethics committees for the Term Breech Trial (TBT), which was a multicenter, international randomized trial that compared cesarean section with planned vaginal birth for specified pregnancies that presented with a breech presentation at birth. The trial involved 2088 women recruited through 121 centers in 26 different countries. The length of time needed to obtain approval from the various ethics review committees ranged from 3 months to 18 months; once the ethics approval had been received, the average time to recruitment was 2.6 months. Ethics concerns arose at several of the sites. At two of the Asia-based sites, the investigators felt that it would be unethical to tell the prospective participants that the doctor did not know which treatment was better because such a statement would arouse anxiety. At some sites, the informed consent process was revised to incorporate procedures for oral consent because of the relatively high illiteracy rates. Similar issues relating to the form of the consent process (oral, written, witnessed) were encountered by van Raak and colleagues (2002) in conducting an international multicenter trial to evaluate the neuroprotective effect of diazepam in acute stroke.

Investigators conducting a multicenter chemoprevention trial in individuals at high risk for lung cancer due to exposure to cigarette smoking and occupational exposure to asbestos also confronted significant delay with respect to the processing of the their protocol by local ethics review committees (Thornquist, Edelman, Goodman, and Omenn, 2002). Between 1988 and 1996, a total of 441 submissions to nine ethics review committees, which averaged more than 50 per year. Approval for protocol revisions

often required more than six months and necessitated significant staff time to track the status of these submissions. Additionally, the requirements of each of the committees differed. Two of the committees found the informed consent form sufficient for the performance of ancillary genetic analyses related to lung cancer, two required new consent forms from the participants or their next of kin, and two required a new consent form for every additional analysis beyond the initial consent.

A number of suggestions have been made to alleviate or eliminate altogether the problems encountered in dealing with multiple review committees. Reliance on national coordinators to facilitate the review process has been found to be helpful (van Raak, Hilton, Kessels, and Lodder, 2002). Where permitted by relevant legislation, reliance on one centralized committee for approval for all sites within a country will also expedite the process (Gold and Dewa, 2005; van Raak, Hilton, Kessels, and Lodder, 2002). The development and use of standardized documents and procedures for their use, electronic access to documentation, and focused training for ethics review committee members may also be critical to improve the process (Gold and Dewa, 2005).

Conclusion

As indicated, multicenter studies bring numerous methodological and economic advantages. However, they also engender various ethical challenges that must be addressed. The resolution of these issues, such as those relating to informed consent, protections for vulnerable persons, the provision of confidentiality, and compliance with the requirements of ethical review committees, may themselves raise additional ethical

and methodological questions. Attention to such issues is a process that likely continues throughout the duration of the study.

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