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48 Abstract

The history of human subjects research and controversial procedures in relation to it has helped form the field of bioethics. Ethically questionable elements may be identified during research design, research implementation, management at the study site, or actions by a study's investigator or other staff. Post-approval monitoring (PAM) may prevent violations from occurring or enable their identification at an early stage. In U.S.-initiated human subjects research taking place in resource-constrained countries with limited development of research regulatory structures, arranging a site visit from a U.S. research ethics committee (REC) becomes difficult, thus creating a potential barrier to regulatory oversight by the parent REC. However, this barrier may be overcome through the use of digital technologies, since much of the world has at least remote access to the Internet. Empirical research is needed to pilot test the use of these technologies for research oversight to ensure the protection of human subjects taking part in research worldwide.

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CRITICAL PERSPECTIVES

Post-Approval Monitoring and Oversight of U.S.-Initiated Human Subjects Research in Resource-Constrained Countries

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Abstract The history of human subjects research and controversial procedures in relation to it has helped form the field of bioethics. Ethically questionable elements may be identified during research design, research implementation, management at the study site, or actions by a study's investigator or other staff. Post-approval monitoring (PAM) may prevent violations from occurring or enable their identification at an early stage. In U.S.-initiated human subjects research taking place in resource-constrained countries with limited development of research regulatory structures, arranging a site visit from a U.S. research ethics committee (REC) becomes difficult, thus creating a potential barrier to regulatory oversight by the parent REC. However, this barrier may be overcome through the use of digital technologies, since much of the world has at least remote access to the Internet. Empirical research is needed to pilot test the use of these technologies for research oversight to ensure the protection of human subjects taking part in research worldwide.

Keywords Ethics · Oversight · Post-approval monitoring · Developing countries · REC

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Ethical Violations in Human Subjects Research

The history of human subjects research is riddled with ethical violations. Some violations in the United States have been well documented such as the Tuskegee syphilis and Willowbrook experiments (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979; Beecher 1966) and the Havasupai case (*Havasupai Tribe v. Arizona Board of Regents* 220 Ariz. 214, 204 P.3 d 1063 [2008]). The increase in U.S.-funded research involving human subjects internationally, especially in resource-constrained settings (RCS), has resulted in a rise in ethical violations in non-U.S. settings and is not as well documented as in the United States. Studies in RCS where ethical violations have been identified include the Trovan trial in Nigeria (Khan 2008), the Yanomami tribe study in the Amazon (Nugent 2001), and genetic studies in China (Sharav 2000).

More recently, details of the Guatemala syphilis study emerged, which led to the development of the Presidential Commission for the Study of Bioethical Issues report titled *Ethically Impossible*: *STD Research in Guatemala from 1946 to 1948* (Reverby 2011; Obama 2010). This report presumably scratches the surface of ethical violations likely occurring in RCS where regulatory oversight of research is still evolving. Clearly the magnitude of ethics violations in RCS—many of which are becoming recognized as prime destinations for U.S.-led clinical trials for many reasons—is not fully known. While groups have begun to explore the issues raised when U.S.-funded research is conducted in RCS (Klitzman 2012), more work is needed. Unfortunately, documentation of poor compliance or noncompliance with the research protocol is limited, with little reference to this in the literature. The literature is, however, rife with reports of ethical misconduct. One such documented report is the shutdown of the Tenofovir trial in Nigeria due to poor adherence to required protocol standards (Mills et al. 2005.

Table 1 lists different types of violations that may occur during the conduct of human research in developing countries, broken down into issues with data, human subjects, and study procedures. These violations vary by severity and may take place even when there are clearly written research protocols, the investigators are highly competent, and the study team is well trained. While some of these violations may occur in research studies in general (e.g., failure to protect data, not obtaining informed consent, changing study protocol/methods without approval), others may be unique to research in RCS. For example, there are several ethical issues that might arise when research is being conducted in one country and the research ethics committee (REC) of the principal investigator's (PI) institution is located in another country. In such a case, the local REC should play a bigger role in study oversight. Issues of particular relevance include how data with identifiers will be transported between countries and how local norms (cultural, social, economic, and political) will be addressed regarding informed consent, adherence to study protocol, and subject compensation. Understanding the local standard of care also will be critical to developing appropriate procedures for maintaining drugs/medications. Moreover, the physical distance between institutions often creates challenges with regard to communication between the PI's REC and the local REC. In addition, RECs in some settings are still evolving, with the main challenge for many being the ability to provide regulatory oversight for a growing portfolio of research studies, thus creating additional opportunities for ethical violations to take place. The violations may be an effect of poor planning by the U.S. institution and be no fault of the host institution.

Table 1 Potential ethics violations in developing countries without PAM

Data issues	Falsification or fabrication Failure to protect data—hard copy and electronic Loss of data when transferred between sites Not retaining data for an appropriate time
Human subject issues	Not obtaining informed consent Limited consideration of local norms (cultural, social, economic, political) when obtaining consent, providing compensation, and conducting study procedures Subjects coerced/pressured to participate (e.g., small villages or cities) Violating subjects' privacy Therapeutic misconception Withholding test results Inadequate or inequitable standards of care Inadequate provision of ancillary care Lack of plans for post-trial access to a successful product Refusing to provide available care or treatment
Study procedures	Over-enrollment Changing randomization assignment without REC approval Not reporting serious adverse events and unanticipated problems Failure to properly maintain drugs/concomitant medications Not maintaining REC approvals

U.S. REC Oversight in Resource-Constrained Settings and Post-Approval Monitoring (PAM)

One of the key functions of RECs in the United States and in many African and Latin American countries is to provide oversight for the research they approve based on regulations set forth in the Common Rule (45 CFR 46 Subpart A, 21 CFR 50 & 56), the Declaration of Helsinki, the International Conference on Harmonisation guidance documents, and United Nations guidelines. RECs are expected to ensure that human research conducted by U.S. investigators in RCS offers the equivalent levels of protection that would be required at the PI's home institution and meets local laws and cultural context. Additionally, it is expected that RECs provide ongoing monitoring of the research to ensure continued human subjects protection. Investigators are expected to report protocol violations and unanticipated problems involving risk to subjects or

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others to the REC. Many RECs in the United States have post-approval monitoring (PAM) programs, which take place after REC approval and help ensure compliance to approved protocols. However, U.S.-initiated studies may not have the resources to conduct PAM in international settings, where local conditions and regulations also must be respected. Countries in RCS may have their own PAM programs, though there is considerable variation internationally.

The goal of PAM is to review active protocols to ensure the research is being conducted in accordance with the approved research protocol and to assure risk to subjects is not greater than originally anticipated. RECs may select studies for PAM or conduct PAM in response to serious adverse events or to a specific request. A PAM program administrator will often visit research study sites in the company of the study PI or his or her designate, observing procedures and noting any inconsistencies with the protocol. The principal investigator often has the opportunity to address any deviations by submitting an amendment to the protocol. The PAM visit is an opportunity for study investigators to request any help they may need. Findings are reported at the next REC meeting. The report of the visit and any follow-up visits are filed in an investigator's REC protocol file. Ideally, the investigator should receive a brief follow-up visit to document completion of any corrective actions related to deficiencies highlighted in the PAM report.

In general, PAM can reduce the likelihood of ethical violations by providing educational training that facilitates best practices and regulatory compliance. The process also can provide significant additional information that enables an institution to be confident that it is meeting both the letter and the spirit of the U.S. federal as well as international regulations developed to ensure the protection of the rights of human participants in research. Moreover, the process could lead to the development of policies and initiatives that provide comprehensive response to misconduct in all countries, including an international framework for PAM (Resnic and Master 2013; Ana et al. 2013).

In the absence of local PAM infrastructure and capability, U.S. PAM activities at research sites in other countries is a major challenge, with distance being the primary obstacle. With limited resources, it may not be practical (staff availability, time, and travel restrictions) or cost-effective (fees for flights, hotel, food) for a U.S. REC to conduct an in-person site visit. Moreover, utilizing local RECs for PAM also has its challenges, as the local REC may lack the capacity to conduct these reviews. Alternative options are needed to address the challenges of conducting research oversight in RCS.

PAM Options and Solutions in Resource-Constrained Settings

PAM in U.S.-initiated studies in RCS should be done jointly with input by the U.S. REC and local REC as a partnership, and always with local regulations prioritized. RECs in some RCS are gradually building their capacity, and with additional training these skills could be utilized for their own conduct of PAM activities. This is ideal, as local researchers, institutions, and communities should be involved in study design and standards. Still, variation in REC experience is vast, which may range from weak to strong RECs, PAM resources built into international networks, and oversight from the federal government. In general, RECs without significant PAM experience should be guided through collaborative training exercises to ensure long-term sustainability to increase research oversight capacity (Cáceres and Mendoza 2009). Regardless of local REC strengths and PAM capability, the REC in U.S.-initiated studies should play a role in PAM of the study as the institution of primary responsibility and should work to support the local REC. In addition, PAM should be of the highest priority when vulnerable populations are involved in the study protocol (Borek et al. 2010).

In the global digital age, much of the world (even most impoverished areas) has at least remote access to the Internet. This allows for the possibility of a digital presence for PAM as an alternative to a physical presence. For example, PAM activities such as web-based educational training and secure file-sharing applications (Howes and D. Wolf 2012 could potentially prevent ethical violations from occurring in the first place by observing training sessions via the web and reviewing research-related documents prior to the commencement of the study protocol to help avert potential violations before they occur. Virtual visits and recordings (via Skype, FaceTime, Google Chat, WebEx) can replace in-person visits by RECs for areas with a reliable Internet connection. Secure file-sharing with Dropbox or cloud computing software can ensure complete transparency. For low-technology areas, a local REC visit or liaison may be appropriate for monitoring. If none of

these options is available, and the local REC is less experienced with PAM or institutional and research team capacity is low, a U.S. REC visit may be most appropriate. In practice, U.S. REC-driven or locally driven PAM policies can include oversight taking place quarterly or annually in human subjects research. Violations or protocol deviations may be identified at an early point and rectified according to REC best practices.

Potential benefits of using technology to facilitate PAM of research in RCS are vast, including reduced expenses in a sparse research funding environment and facilitation of communication and ethics education with the local RECs and with investigators, creating more of a collaborative process that may further help reduce ethical violations. Funds can be written into research grants to support the technology needed for PAM as well as to provide human subjects and ethics training to research collaborators in non-U.S. countries. This should be considered a requirement for future federally funded international research.

The use of digital technology for PAM would eliminate costs associated with domestic travel and, if needed, U.S. RECs travelling to distant sites. The technology would, however, still require that REC members invest time for the process and the building of the human capacity of the PAM administrative officer with requisite interpersonal and communication skills to interact constructively with researchers. The use of digital technology in RCS also comes with its own challenges. These include funding the technology, ensuring access to (reliable) Internet connectivity, maintaining records electronically, and managing different time zones for international communication. Also, the use of digital technology for PAM does not address issues of trust and respect for the local REC in performing its own oversight.

Next Steps

Investment in the piloting of the use of digital technology for PAM is important. In 2012, the Harvard School of Public Health reported on the use of web-based conferencing to conduct PAM with investigators in low- and middle-income countries. It examined the advantages associated with PAM, including promptly identifying protocol deviation and record-keeping deficiencies and addressing these issues (Howes and D. Wolf 2012).

International standards for the proper conduct of PAM in RCS are needed. PAM should be prioritized and funds for this monitoring should be made available. Considering the time it took to learn about the Guatemala syphilis experiments, it is imperative to develop methods to prevent potential violations from occurring. Unfortunately, post-approval noncompliance will occur despite even the best-run PAM program with or with our digital technology. The documentation of these violations is important for many reasons, including the provision of helpful information to assist in the design of the best use of digital technology for PAM to address these on-site challenges. Also, there is a need for empirical research to further explore the technologies currently available to enhance the ability of RECs and other research regulatory agencies to protect research subjects.

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