

Urgent Ethical Challenges in Human Subjects Protection

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There is widespread agreement that the oversight of human subjects in research is inadequate to fully protect the safety and well-being of research participants (ACHRE, 1995, Shamoo, 1997, 2000, 2001, NBAC, 1998, Emanuel et al, 2004). Unfortunate individual cases involving death or other harm to research participants, suspension of research at prominent institutions, research misconduct, financial improprieties, and other high-profile cases have sometimes dominated the discussion (Bloomberg, 2005). But, underlying these cases are structural shortcomings in the system. Our society continues to need more and more volunteers for human research. This increase in the number of human subjects could exacerbate current problems in the system. Institutional inertia, lack of consensus, complexity and sometimes conflicting priorities of the responsible parties from government, research institutions, industry and other organizations are delaying reform. In the absence of reform, serious problems have emerged in five important areas:

Gaps in Regulation

Federal regulations do not apply to all research studies involving human subjects. The number of human subjects participating in unregulated research is not known. Over 20 million human subjects participate in research in the United States at any time, with about half in interventional drug studies (Shamoo, 2001). Therefore, even if unregulated research represents only a small fraction of studies, a significant number of human subjects enroll in research studies without any regulatory coverage. The number of human subjects participating in unregulated research will undoubtedly increase given the growth in funding of studies by for-profit and private non-profit entities in controversial and potentially dangerous areas such as stem cell research, reproduction, complex innovative surgical procedures, and nutraceuticals.

The current patchwork of U. S. federal regulations governing clinical research has evolved over the past 30 years based on legislative acts and recommendations of various federal commissions (Belmont Report, 1979, NBAC, 2001, Shamoo, 2001). The primary regulations enacted in 1981 and in 1991 are the "Common Rule" (45 CFR 46) (2006) and its companion regulations for 17 federal agencies, including the Food and Drug Administration (FDA). These regulations cover human subjects enrolled in research funded by the federal government or part of a request for a license for marketing a drug, biologic or medical device in the United States. The Office for Human Research Protections (OHRP) oversees research funded by the federal government. The FDA oversees research intended to support marketing applications (21 CFR 50, 54, 56, 312 and 314). Human subjects research that is not funded by the federal government and is not intended for an application for a marketing license from the FDA is not regulated. Many pre-Phase I, Phase IV, and investigator-initiated studies fall in this category.

Institutions conducting research funded by the federal government are required to file a Federal Wide Assurance (FWA) (2006), with a voluntary option to comply with federal regulations in all research conducted at the institution, regardless of funding source. Many research institutions have taken this option, but others have not. The American Association of University Professors (AAUP, 2006) found that 164 institutions – including Harvard University, Princeton University, the University of Chicago, and the University of California,

Berkeley – did not elect the option. In contrast, the Animal Welfare Act (1966) requires federal regulation of all animal research, regardless of funding source. Recently, Maryland became the first state to require federal protections for human research subjects regardless of the funding source (Maryland Laws, 2002).

Numerous federal legislative reforms have been proposed to require that all human subject research comply with federal regulations (Research Revitalization Act of 2002. S 2060, 107th Congress; Human Subject Research Protection Act of 2002. H.R. 4697, 107th Congress). To date, none of this legislation has been enacted.

No Mandatory Training of Investigators

Responsible research with human subjects requires specific education and training in ethics and regulatory compliance. However, it is unknown how many principal investigators have received the necessary training. Professional certification is not required by law or custom, so only a few hundred investigators, to our knowledge, have obtained it. Other health-related professions, such as physicians, nurses and pharmacists, have formed state professional societies that administer licensing exams and require continuing education and compliance with codes of professional behavior. Although clinical research relates to these professions, it has very different requirements for knowledge and skills.

Two places in the federal system of regulation of human research mention a voluntary education requirement:

“...the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.” (45 CFR 46.107(a) and 21 CFR 56.107(a))

“...I recognize that providing all research investigators, IRB members and staff, and other relevant personnel with appropriate initial and continuing education about human subject protections will help ensure that the requirements of this Assurance are satisfied.” (FWA, 2006)

The investigator plays the key role in protecting human subjects, but typically receives less training than IRB members and most personnel, such as research coordinators, involved directly in research. There is a glimmer of hope on the horizon. At the 2006 Public Responsibility in Medicine and Research (PRIM&R) national meeting, Bernard Schwetz, Director of OHRP, stated that improved training and mentoring of investigators in ethics and regulatory compliance is one of OHRP's top priorities.

No Universal and Uniform Adverse Event Reporting

Adverse event reporting and monitoring are critical in the conduct of clinical research. Unfortunately, there is no universal, uniform and mandatory requirement to report adverse events (Shamoo, 2001, Shamoo and Strause, 2004). Instead, there is a patchwork of regulatory requirements with unclear definitions and timelines. For example, the Common Rule does not even mention the terms “adverse event” or “report.” FDA regulations mention adverse event reporting in seven places, but with differing timelines and definitions.

The number of adverse events is very large, and may exceed 500,000 per year (Shamoo, 2001). Moreover, the number of deaths could exceed thousands per year. However, only a small fraction is reported (Shamoo, 2001), and a much smaller fraction attributed to participation in the research, particularly in subjects with severe co-morbidities. Many have commented on the inability of local IRBs to provide meaningful oversight of adverse events in multisite studies where the committees do not have sufficient information to interpret adverse event reports in the context of the complete study (Emanuel et al, 2004). Under-

reporting of deaths and unanticipated events threatens to undermine the regulatory oversight of research. Therefore, a more universal and uniform system for reporting adverse events would serve the goal of human subjects protection.

Inadequate Regulation Concerning Children

Children are afforded special protections under federal regulations. The regulations in Subpart D of 45 CFR 46 define four categories: 404, 405, 406 and 407. Section 404 deals with no greater than minimal risk; Section 405 deals with greater than minimal risk, but with direct medical benefits; Section 406 deals with a minor increase over minimal risk ("the risks of daily life"), with no direct medical benefits but with results that are important for the "child's disorder or condition"; and Section 407 deals with research that does not qualify for approval in the first three categories, and must be approved by the Secretary of Health and Human Services after a public hearing and special 407 panel recommendation.

Application of the federal risk and benefit categories is often difficult. The problem primarily arises in category 406. Federal guidelines do not define "the risks of daily life," nor do they describe what constitutes "a minor increase over minimal risk." More concerning is the ambiguous requirement that "the study results are important for the child's disorder or condition." Application of this requirement is left to the unaided interpretation by thousands of IRBs. Indeed, Shah and colleagues demonstrated substantial variability in the assessment of risk and benefit categories for pediatric research by IRB chairs (Shah et al, 2004). In 2005, an Institute of Medicine report (2004) recommended clarification and strict rules for interpretation. The Secretary's Advisory Committee on Human Research Protections (SACHRP) advocated the use of component analysis, whereby each procedure in a study is evaluated independently in terms of potential benefits and risks to the child (SACHRP, 2005), and stated, "Different procedures in a single trial may be approved or disapproved under different Subpart D categories."

Many authors have commented on the difficult ethical issues of pediatric research (Kodish, 2005, Shamoo and Tauer, 2002, Kopelman, 2004, Nelson and Ross, 2005). Vaccine development and pharmacokinetic and pharmacodynamic studies in children may be particularly affected by the component analysis approach to the application of category 406. An unintended societal consequence of this stricter protection in research may be greater exposure of children to harm in clinical practice from drugs developed and tested in adults and used "off label" in children. Unfortunately, so far there has been no regulatory or guidance remedy.

Lack of Oversight and Monitoring of Research Abroad

All of the problems mentioned above apply to research conducted by U.S. sponsors in developing countries. In addition, there is one unique additional challenge.

For research conducted at U.S. sites, the sponsor must submit an Investigational New Drug Application (IND) and receive approval (technically, non-denial) from the FDA prior to commencing the trial. In contrast, the FDA accepts or rejects data from a foreign site, regardless of whether the sponsor is based in U.S., after the research has been conducted. At that point, it is too late for the FDA to influence protection of those human subjects.

Moreover, the current system of relying on human subjects protections in developing countries that would be inadequate for research in the United States agencies is troubling (Shah, 2006). OHRP and FDA should hold research abroad to comparable standards as research in the United States. We should respect local cultures, but minimize the sacrifice of human subjects protections.

Conclusion

The patchwork of human subjects protections urgently needs reform. It is imperative that the federal government, in collaboration with professional organizations, advocacy groups, academia and industry, address structural shortcomings before expanding clinical research, especially in the developing world, makes the above problems even more serious.

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