Virtual Mentor
American Medical Association Journal of Ethics
April 2009, Volume 11, Number 4: 311-321.

POLICY FORUM
The History and Role of Institutional Review Boards
Margaret R. Moon, MD, MPH, and Felix Khin-Maung-Gyi, PharmD, MBA

Editor's Note:
Institutional review boards (IRBs) have evolved since the middle of the 1960s as independent reviewers of research protocols that, if approved, will be funded by the U.S. government or will test drugs or devices regulated by the Food and Drug Administration. As their name suggests, IRBs began and developed at academic research institutions. More recently, independent, so-called "central" IRBs have come on the scene. The following two articles recap the history of IRBs and examine the strengths and weaknesses of local, institution-affiliated IRBs and central, non-affiliated IRBs.

A Useful Tension
Margaret R. Moon, MD, MPH

"Act in such a way that you treat humanity, whether in your own person or in the person of any other, always at the same time as an end and never merely as a means to an end" [1].

Immanuel Kant's second maxim defines the tension that drives and bedevils IRBs. Human-subjects research uses humans as subjects, as a means to an end. The imperative that it is never *merely* as a means, but always *also* as an end in themselves, makes IRBs necessary.

The history of human-subjects research is replete with horrid examples of what happens when investigators fail to respect humans as ends in themselves. Even after the Nuremberg trials exposed the Nazi war crimes and the Nuremberg Code provided a clear statement of standards for research on human subjects, unethical research programs continued to be designed and conducted [2]. In the United States, the Willowbrook study of hepatitis transmission in a hospital for mentally impaired children, Tuskegee Syphilis Study, Fernald State School trials using radioactive minerals in impaired children, and Jewish Chronic Disease Hospital case in which chronically ill patients were injected with cancer cells to monitor rejection, are infamous examples of egregiously unethical research designed and conducted long after the Nuremberg Code was in place. In each of these studies, investigators were confident that the ends of research justified the means.

The National Research Act of 1974, passed in response to growing concern about the ethics violations in research, created the National Commission for the Protection of

Human Subjects of Biomedical and Behavioral Research. The Belmont Report of 1974 was the commission's summary of the ethical principles that form the basis of acceptable human-subjects research, and the three foundational Belmont principles were:

- *Respect for persons*. This principle includes both respect for the autonomy of human subjects and the importance of protecting vulnerable individuals.
- *Beneficence*. More than just promotion of well-being, the duty of beneficence requires that research maximize the benefit-to-harm ratio for individual subjects and for the research program as a whole.
- *Justice*. Justice in research focuses on the duty to assign the burden and benefits of research fairly.

Recent questions about the role of IRBs and their structure and affiliations are easier to understand in light of their historical and ethical foundations.

The essential conflict in research is the duty to avoid allowing the ends to justify the means. Individual investigators, although generally dedicated to promoting the well-being of their subjects, may not be well placed to identify and avoid the influence of inherent conflicts of interest. IRBs have to be independent from the investigator and the rewards of research. Arguments about the appropriate location of IRBs: so-called "central" IRBs versus "local" IRBs focus on the board's level of independence.

Central IRBs are usually for-profit ventures and receive payment from investigators for their services. Arguments against central IRBs maintain that these ventures are open to influence from the investigators who pay them and that their income derives from their ability to please the investigators, which may pressure the board to quick and easy approval.

Local IRBs are functions of the academic institutions that conduct research. Arguments against local IRBs point out that the academic institution itself has conflicts of interest about research. The institution benefits from the research dollars and the prestige associated with a far-reaching and well-funded research agenda. Local IRBs are under pressure to approve research to protect the financial resources and power of the institution.

Both sets of arguments are valid critiques of the risks in their respective structures. Neither structure is free from potential conflict, and neither is inevitably tainted. Other questions might be more reasonable. Are there benefits to locating an IRB within the academic institution conducting research that are not attainable in a central IRB structure, and if so, how can local IRB structure and function be optimized?

Advantages of Local IRBs

Local IRBs, through the academic institutions that house them, reflect those institutions' complex relationships with their communities. Academic institutions are not virtual, they are brick-and-mortar structures that exist within a geographic

community. The relationship between the institution and the community usually involves clinical care, education, and employment in addition to research. The interests and experiences of the community and academic institution are not easily separable. One of the most productive tensions within local IRBs reflects these shared interests. Subjects of research are often also patients in the hospital or clinic, family members of patients, students in the university, or other community members. Problems arising within the research setting affect the community, the standing of the institution within the community, and eventually the trust and respect between clinician and patient. These relationships are critical to the mission of the institution, as is the flow of research dollars and accompanying prestige. Local IRB members are directly affected by the relationship between "town and gown" and are well placed to want to protect it.

Within an institution, researchers are also recognized as clinicians, educators, and colleagues. The track record of a particular investigator with regard to other aspects of professional practice may be known to a local IRB in ways that are not available to central IRBs. Concerns that may impact the investigator's ability to conduct research appropriately can be identified and monitored more effectively by local IRBs. Reliance on local IRBs makes it difficult for investigators to "shop" challenging protocols to IRBs they think will view the protocols favorably.

Human subjects are also patients, colleagues, students, and community members. Local IRBs may be best placed to consider human protections in the wider sense of the subjects' experience and to incorporate the impact of research on communities and the relationships among subject, community, and institution as part of the review. Local IRBs emphasize the institution's responsibility for the whole of the research enterprise and all of its ramifications.

Disadvantages of Local IRBs

Proponents of central IRBs argue that the nuanced view described above makes for slow and inconsistent reviews. Particularly with multicentered trials, local variations in review and requirements create havoc [3]. This is probably a valid observation, although not an unavoidable problem. However frustrating, the fact that the research itself takes place in a local setting, is conducted by local researchers, and enrolls local subjects ought to make an institution consider carefully before yielding its duty to protect subjects to an outside body.

Improving Local IRBs

If, as I argue, the local IRB structure offers something valuable, how can its function be optimized to best fulfill the duty of protecting human subjects? Three areas worthy of improvement are IRB membership, evidence base for IRB review, and IRB mission.

IRB membership. The Office for Human Research Protections' guidelines on membership for IRBs are reasonably loose. IRBs must have at least five members including at least one member:

- Whose primary concern is scientific.
- Whose primary concern is nonscientific.
- Who is not affiliated with the academic institution.

The experience and expertise of members must be sound and relevant enough to promote respect for the board's advice in safeguarding the rights and welfare of human subjects. Membership should reflect the types of research the board reviews and should avoid any semblance of discrimination. Two specific areas of IRB membership deserve discussion: the role and use of community representatives, and the need for ethics expertise on IRBs.

Many academic (local) IRBs include a person who is asked to represent the interests of the community as a non-affiliated member. While this role can be extremely helpful, the usual process of identifying and engaging community members has not been conducive to meaningful involvement. Community members report that their main function seems to be to simplify the language of consent forms. Few have had significant training and many report feeling intimidated or disrespected by other IRB members [4]. Most importantly, the task of representing "the community" may be impossible given most communities' diverse interests and vulnerabilities [5]. Effective community representation may be necessary to help IRBs meet their mandate, but this requires a more directed and goal-oriented approach. Instead of relying on individual representatives, the IRB function might be better supported by well-organized and consistent use of community advisory boards for research that is (1) of particular interest to the local community, (2) of concern to a specific and identifiable subset of the community, or (3) community-based research that is nontherapeutic. Community advisory boards are able to represent a variety of stakeholders within the community, reducing reliance on an individual community member. They can be created for a specific protocol, including members with related experience or specific representation of vulnerable groups. Functioning in parallel to the IRB's, they can present reports and recommendations to the IRB without increasing the IRB workload.

Although the function of an IRB is fundamentally to answer questions about ethics, there is no requirement that IRBs include members with specific ethics expertise. This raises challenges for IRBs because, as the NIH explains:

> 45 CFR Part 46 is not a set of rules that can be applied rigidly to make determinations of whether a proposed research activity is ethically "right" or "wrong." Rather, these regulations provide a framework in which investigators and others can ensure that serious efforts have been made to protect the rights and welfare of research subjects [6].

With or without expertise, IRB members engage in discussion of complex questions about conflicting moral obligations such as the duty to: (1) protect human subjects while respecting their autonomy to engage as willing subjects, (2) consider the limits of parental authority to consent to research on their children, and (3) balance current

harms against future benefits when incompetent subjects are involved. Ethics expertise can be helpful to an IRB, particularly in identifying and analyzing conflicting moral obligations, considering research-ethics literature, encouraging a consistent approach to ethics issues, noting and clarifying the impact of the personal moral values of the IRB members, and explaining the ethics-related conclusions of IRB reviews. An IRB without ethics expertise among its members may benefit from consulting ethicists for particularly complex cases.

Evidence base for IRB review and clarifying the mission. IRB members volunteer their service. IRBs review complex research from a broad range of clinical and scientific disciplines, with single protocols sometimes running hundreds of pages in length. Careful review of protocols requires substantial clinical understanding and willingness to read deeply. Given these demands, some have unrealistic expectations of their members who face competing professional demands.

IRBs are experiencing a drift in mission that draws members away from the duty to ensure the fundamental protection of human subjects. "Mission drift" has two main causes, an interpretation of oversight requirements that employs the widest connotations of "research" and "risk," and an increasing focus on process and documentation that takes time away from thoughtful review of important protocols. The definition of research in the federal guidelines is broad enough to include a vast array of efforts to produce generalizable knowledge, from oral histories to "first in human" drug trials. While there is potential for risk to human subjects in all such efforts, institutions that rely on the same IRB to identify and oversee all potential risks in types of research can easily overwhelm the board. Definitions of risk are both extensive and incomplete in the federal guidelines. Risks to human subjects are both biomedical and behavioral, and the latter can be psychological, social, and economic. Categorization of risk following the federal guidelines is open to wide and variable interpretation by individual IRBs. Better definitions of types of risk and data to encourage consistency in applications would help IRBs limit the types of research that require full IRB review and make reviews seem less capricious and unpredictable [7].

The seemingly inevitable expansion of process and documentation comes at the expense of meaningful dialogue; this phenomenon is common enough in institutions. In an overburdened IRB system, however, the result is "simultaneous overregulation and underprotection" [8]. Uncertainty about regulations and fear of disciplinary action encourages investigators to over report safety issues. HIPAA guidelines add layers of documentation with minimal functional benefit; compliance requirements of the IRB accreditation process compel unrealistic documentation; regulations require full IRB review of minor changes in massive protocols; and regulations on consent forms encourage a focus on structure over function. These are just a few of the influences that drive IRBs toward an unproductive balance of process over protection [9].

While the problems facing local IRBs are substantial, they are not inevitable. Local IRBs offer a unique benefit to researchers, institutions, and communities, most specifically to the relationships that bind these three entities. The defining role of IRBs, to protect human subjects of research, can and ought to be preserved and reinforced. Protecting local IRBs may require a review of IRB procedures with an eye toward a better business model with a more narrowly defined role and efficient process, reasonable salary support for IRB members, the development of better data upon which to justify risk decisions, and better use of community representation and ethics expertise. These changes should bring IRBs back toward their primary mandate and help preserve the unique value of local IRBs.

References

1. Kant I. *Grounding for the Metaphysics of Morals.* 3rd ed. Indianapolis, IN: Hackett Pub. Co; 1993: 30.
2. National Institutes of Health. Nuremberg Code. 2009. http://ohsr.od.nih.gov/guidelines/nuremberg.html. Accessed March 2, 2009. Reprinted from: *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10.* Washington, DC: US Government Printing Office; 1949.
3. Silverman H, Hull SC, Sugarman J. Variability among institutional review boards' decisions within the context of a multicenter trial. *Crit Care Med.* 2001;29(2):235-241.
4. Sengupta S, Lo B. The roles and experiences of nonaffiliated and non-scientist members of institutional review boards. *Acad Med*. 2003;78(2):212-218.
5. Catania JA, Lo B, Wolfe LE, et al. Survey of U.S. Human Research Protection Organizations: workload and membership. *J Empir Res Hum Res Ethics*. 2008;3(4):57-69.
6. National Institutes of Health. Guidelines for the conduct of research involving human subjects at the National Institutes of Health. 2004. http://ohsr.od.nih.gov/guidelines/GrayBooklet82404.pdf. Accessed March 9, 2009.
7. Wendler D, Belsky L, Thompson KM, Emanuel EJ. Quantifying the federal minimal risk standard: implications for pediatric research without a prospect of direct benefit. *JAMA*. 2005;294(7):826-832.
8. Gunsalus CK, Bruner EM, Burbules NC, et al. Mission creep in the IRB world. *Science*. 2006;(312)5779:1441.
9. Fost N, Levine RJ. The dysregulation of human subjects research. *JAMA*. 2007;298(18):2196-2198.

Margaret R. Moon, MD, MPH, is the Freeman Family Scholar in Clinical Medical Ethics in the Berman Institute of Bioethics at Johns Hopkins University in Baltimore. She is also an assistant professor in the Division of Pediatrics and Adolescent Medicine at Johns Hopkins University School of Medicine.

Local and Central IRBs: A Single Mission
Felix Khin-Maung-Gyi, PharmD, MBA

The evolution of protection for human-research subjects in the United States is rooted in the tragic outcomes of unregulated, unethical research conducted worldwide [1-4]. Similarly, oversight of the development, marketing, and sale of safe foods and drugs has evolved into a more regulated environment following the revelation of several catastrophic and heartbreaking events associated with the consumption of mislabeled or adulterated products [5, 6].

In the United States, compliance with federal regulations is mandated if research involves federal funding or if a product (drugs, devices, biologics) or product component is regulated by the Food and Drug Administration. The federal regulations address the responsibility of a sponsor, principal investigator, and an independent reviewer—the institutional review board (IRB). Typically, the sponsor is a government agency or company that pays to conduct the research. The principal investigator carries out the research and collects the data. The role of the IRB is to review and approve proposals for research that involves human subjects to assure the protection of their rights and welfare before the research is undertaken. Following the initiation of the research, the IRB must continue to provide oversight at intervals appropriate to the degree of risk associated with the research, but not less than once per year.

Historical landmarks on the road leading to the current U.S. regulations include the Nuremberg Trials (and the Nuremberg Code), Willowbrook hepatitis study, Jewish Chronic Disease Hospital case, and Tuskegee Syphilis Study, among others. The most notable from a regulatory-reform perspective is the legacy of the U.S. Public Health Services' Tuskegee Syphilis Study, formally entitled Tuskegee Study of Untreated Syphilis in the Negro Male, conducted in rural Alabama. This deceptive and unethical study, which began in 1932 and terminated in 1972, was not an interventional study but observational in scope and intent. It denied treatment to infected individuals even after the commercial availability of penicillin—a known and accepted treatment for syphilis. Following the publicity of the study, the National Research Act became law in 1974, and prompted the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

The commission produced The Belmont Report, which identified ethical principles that served as the foundation for the regulations as we apply them today—the three being: respect for persons, beneficence, and justice [7]. Respect for persons allows individuals to be self-directed and make informed, voluntary decisions about whether they wish to participate in research. Fundamentally, this respect for individual decision making is operationalized by obtaining and documenting informed consent from the prospective subject. Beneficence assesses the risks of participating in research against the benefits a participant might realize, recognizing the obligation of the researcher to minimize risks while maximizing the benefits of participation. The

principle of justice, when applied to selecting subjects and populations for research, directs investigators to seek those who would benefit from the outcome of the research and to not impose undue risks on those who would not otherwise be helped from the research. A violation of the principle of justice occurred when prisoners were asked to participate in dermatologic research for cosmetic manufacturers chiefly because they were a captive group and willing to participate [8].

The Belmont Report also helped define the distinction between clinical research and clinical practice in the following manner:

> For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective [9].

The current regulatory definition of research is accepted to be activities that lead to contribution of generalizable knowledge and that require overview by an independent body (IRB) for the protection of human-research subjects.

Regulatory authority of the IRB includes the authority to approve, disapprove, or require modifications to some aspect of the application or protocol before granting approval of the research it oversees. Applications that an IRB disapproves may not be approved by another individual. Research that an IRB approves, however, may be disapproved by a duly designated official of the institution. Criteria an IRB uses to make its determinations are described in the regulations and can be summarized as addressing aspects of the research that:

- Minimize risks to subjects.
- Include only those risks to subjects that are reasonable in relation to anticipated benefits, if any.
- Assure the equitable selection of subjects.
- Ensure respect for a subject's rights by having each subject, or his or her legally authorized representative, give informed and voluntary consent that is appropriately documented.
- Ensure that the research plan makes adequate provisions for monitoring the research.
- Ensure that there are adequate provisions to protect the privacy of a subject and maintain the confidentiality of data.

- Ensure that additional safeguards have been included when some or all subjects are likely to be vulnerable and there is a potential for coercion or undue influence.

What the regulations don't mandate is where the IRB is located and *how* it carries out its duties. Traditionally, IRBs were located where the investigator conducted research, such as an academic medical center. But the research enterprise has evolved so that IRBs are now affiliated with community hospitals, associations providing funding for research, and regulatory agencies. Central or independent IRBs are not affiliated with any researcher or research institute.

All types must comply with the same regulations governing the protection of research subjects. Central and independent IRBs came into existence because researchers who had gravitated away from the academic medical centers and toward the community and private practice maintained their research interests. These investigators primarily conducted pharmaceutical, device, and biologics company-sponsored research but did not have access to an IRB. The independent IRBs fulfilled that requirement, enabling researchers outside the academic medical systems to conduct research in compliance with the regulations. Recent experiences and evaluations of the human- research protections systems have suggested that a centralized oversight system might be more appropriate, especially given the globalization of research [10-12].

The emergence of the various models of IRBs has raised concerns about a range of potential conflicts of interest, particularly for those IRBs that provide oversight for a fee. In the present environment, the role of accreditation by the Association for the Accreditation of Human Research Protections (AAHRP) has helped to formalize standards that research organizations can measure themselves against voluntarily. To attain AAHRP accreditation, IRBs and research organizations, independent or affiliated with teaching medical centers, must demonstrate and document compliance with applicable regulations and standards of practice. While the accreditation process is an optional supplement to industry and regulatory oversight, some industry thought-leaders have embraced it as the acceptable standard for conducting appropriate research [13].

In summary, oversight of human-research protections, and specifically the IRB, has evolved to accommodate research that is being conducted in sectors outside the traditional academic setting. While one might assume that the users of independent IRBs may "shop" for the desired answer from existing organizations, the FDA concluded that there is no evidence to suggest that there is abuse of "answer shopping" [14].

References

1. Katz J. *Experimentation with Human Beings; The Authority of the Investigator, Subject, Professions, and State in the Human Experimentation Process.* New York, NY: Russell Sage Foundation; 1972

2. Levine RJ. *Ethics and Regulation of Clinical Research*. Baltimore, MD: Urban & Schwarzenberg; 1986.
3. Annas GJ, Grodin MA. *The Nazi Doctors and the Nuremberg Code*. New York, NY: Oxford University Press; 1992.
4. Jones JH. *Bad Blood: The Tuskegee Syphilis Experiment.* 2nd ed. New York, NY: Free Press; 1993.
5. Sinclair U. *The Jungle*. New York, NY: Doubleday, Jabber & Company; 1906.
6. Hilts PJ. *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*. New York, NY: Alfred A. Knopf; 2003.
7. National Institutes of Health, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. 1979. http://ohsr.od.nih.gov/guidelines/belmont.html. Accessed March 3, 2009.
8. Hornblum AM. *Acres of Skin, Human Experiments at Holmsburg Prison*. New York, NY: Routledge; 1998.
9. National Institutes of Health et al., 5.
10. Emanuel EJ, Wood A, Fleischman A, et al. Oversight of human participants research: identifying problems to evaluate reform proposals. *Ann Intern Med.* 2004;141(4):282-291.
11. Glickman SW, McHutchinson JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med*. 2009;360(8):816-823.
12. Burman WJ, Reves RR, Cohn DL, Schooley RT. Breaking the camel's back: multicenter clinical trials and local institutional review boards. *Ann Intern Med.* 2001;134(2):152-157.
13. BNA, Inc. Economy, new administration could affect OHRP regulatory action, goals, official says. *Medical Research Law Policy*. March 4, 2009.
14. Department of Health and Human Services, Food and Drug Administration. Institutional review boards: requiring sponsors and investigators to inform institutional review Boards of any prior institutional review board reviews; withdrawal. 2006. http://www.fda.gov/OHRMS/DOCKETS/98fr/E6-357.htm. Accessed March 9, 2009.

Felix Khin-Maung-Gyi, PharmD, MBA, is founder and CEO of the Chesapeake Research Review and an expert in the area of human-subject protection both in the United States and abroad. Dr. Gyi was appointed as a charter member of the Secretary's Committee on Human Research Protections (SACHRP) of the U.S. Department of Health and Human Services in 2003, and is currently a member of a subcommittee of SACHRP designated to review the interpretations and impact of regulations on the burdens and efficiencies of human-research protections. Dr. Gyi is coauthor of *Ethics of the Use of Human Subjects in Research,* chapters in other books, and articles in *DIA Journal*, *Applied Clinical Trials*, and *Research Practitioner*.

Related in VM
Institutional Review Board Liability for Adverse Outcomes, April 2009

The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.