Ethics in Public Health Research

Time, Place, and Consciousness: Three Dimensions of Meaning for US Institutional Review Boards

Sarah B. Putney, JD, and Sofia Gruskin, JD, MIA

In the past few years, US federal agencies governing research with human subjects and institutional review boards have taken a higher-profile path than ever before, both at home and internationally. This trend carries profound significance for US-based institutions and has implications also for the rest of the world.

What does this critical moment of heightened federal scrutiny mean for the workings of US institutional review boards? We examined board activity across 3 dimensions: time, place, and consciousness. We conclude that although institutions in all areas of biomedical and social science research are adapting their practices, the field of public health is especially well positioned to adapt to, and succeed in, new efforts to ensure protection of human research subjects. (*Am J Public Health.* 2002;92:1067–1070)

TIME

RECENTLY, DRAMATIC

shutdowns of research at US-based institutions by the Food and Drug Administration (FDA), the federal Office for Human Research Protections (OHRP), and OHRP's predecessor, the Office of Protection against Research Risks, have brought heightened attention to human subject protections. The institutional assurance mechanism is central to how a shutdown can happen.

Institutions are licensed to use federal funds to conduct research with human subjects through an assurance that is granted on the condition that the institution abide by certain terms. The funding agency can partially restrict or suspend the assurance if there is a failure in compliance on the part of the grantee. Suspension includes revoking the privilege of using federal funds to conduct research with human subjects.[1,2] Institutions are given an opportunity to remedy systemic failures that may be affecting institutional review board (IRB) operations before any suspension or shutdown occurs. The self-assessment that led to the drafting of this article was, in fact, catalyzed by an OHRP investigation into Harvard School of Public Health genetic epidemiological studies conducted in urban and rural China.

The tragedy of human deaths prompted shutdowns at the University of Pennsylvania[3] and Johns Hopkins.[4] These public punishments sent shock waves through US institutions and gave IRBs, at these institutions and elsewhere, increased internal institutional attention by providing real examples of the willingness of the government to exercise its power to secure the integrity of the system. Survivors of shutdowns are now striving to demonstrate, within their institutions and beyond, the proper ways to conduct IRB business. At IRB conferences, these individuals can be found speaking on panels with representatives of OHRP, delivering the message that the time to conduct quality improvement is *now.*

Curiously, the urgency that manifests in institutional responsiveness to the shock of shutdowns expresses the redemptive quality of IRB work. Indeed, IRBs owe their existence to efforts to reckon with the most notorious abuses of power in human studies in recent generations—the Nazi doctors, the Tuskegee Syphilis Study—as well as many lesser-known studies gone wrong.[5] The history of each of these studies is complex, raising questions about investigators' intentions, assumptions, and conflicts between conscience and rationalization, which belie the easy moral authority of hindsight.[6,7] Yet a common element among them is that researchers acted either without a legal system for enforcement of ethical behavior (as with the Nazis and the Tuskegee Study) or in spite of one.

The 1970s marked a passage into a new era of efforts to do better by human subjects, especially those recognized to be vulnerable. In 1972 the Tuskegee study was finally terminated by the US Department of Health, Education, and Welfare after the public responded to media exposure.[8]

In 1974 the federal regulations were promulgated,[9] and in 1978, the Belmont Report was issued following the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[9] (The National Commission was created by the National Research Act [Pub L 93-348] in 1974. The federal regulations known collectively as the Common Rule [45 CFR §46.101 et seq] superseded the 1971 guidelines of the Department of Health, Education, and Welfare.) The federal regulations protect certain categories of "vulnerable populations" through special provisions: pregnant women, fetuses, and neonates in subpart B, prisoners in subpart C, and mi-

nors in subpart D of Title 45, CFR §46. Other groups considered vulnerable to coercion and undue influence, who do not have the benefit of a regulatory subpart, include persons with cognitive impairment, persons with low literacy skills, and the poor and politically disenfranchised (see 45 CFR §46.111(b)).

Although the public has been shaken by shutdowns and institutions complain about the regulatory burdens, the IRB system is likely to endure. It remains an appealing model because it expresses aspirational values such as individual autonomy and justice. Its operations are meant to be conducted in quasi-independence from its institutional parent and driven by conscience and rational debate. An IRB has a reasonably democratic, jury-like character. As prescribed by the Common Rule, it must consist of no fewer than 5 members, including both men and women. These members must possess both scientific and nonscientific skills and expertise and must reflect the ethnic or cultural diversity of the local community at large.[10,11] At least one member must be unaffiliated with the institution.[12]

The system requires that members, like a jury or an electorate, inform themselves, debate issues, and vote.[13] A simple majority prevails. Conflicts of interest require disclosure and recusal.[14,15] An IRB must explain its reasoning to the affected investigator if it votes to disapprove a protocol, and the investigator must be given the opportunity to respond.[16] In practice, IRBs are highly collaborative bodies; rarely is a decision made by only one person without the input of others.

"The time is now" means that now, IRBs have the responsibility to give painstaking attention to every protocol, documenting compliance rigorously. Yet urgency can meet logistical blocks—shortages of staff, space, money—that can translate into delays and crises. The costs involved in running IRBs effectively are significant, and the financial implications for institutions with limited resources have not been sufficiently considered.

Unless an industrial sponsor can be tapped (usually done through a contract budget item), institutions theoretically pay the costs of IRBs out of overhead revenue. Currently, grants do not allow for IRB costs as separate from indirect costs. The National Institutes of Health (NIH) has issued a request for applications in which it announced that $28.5 million in grant funding is available to improve institutional IRBs.[17] While this is apparently only a one-time offer, it may be of immediate use in helping to strengthen existing mechanisms and processes for eligible institutions.

This financial offer may well signal an increased effort toward collaboration and outreach by federal regulators. OHRP director Greg Koski introduced in 2001 the motto "Doing it right . . . together," which has become a hallmark of his directorship. Since then, he has rolled out a number of programs to activate the partnering role of the government, including a quality improvement unit,[18] a simpler assurance system, increased staff, and more town meetings and workshops.[19] The challenge for IRBs is, and will continue to be, "doing it right" manageably, in a way that satisfies all parties: human subjects, federal regulators, investigators, sponsors, and scientific reviewers. Doing it right means at a minimum that nothing bad happens, an outcome that is tricky to measure. The redemptive plays out as preemptive.

PLACE

Just as the time is *now*, US IRBs are increasingly finding that their place includes wherever it is that their investigators go. Everywhere US-funded investigators are engaging in human research, they and their IRBs are increasingly coordinating their approach to the ethical basics with the "local research context."[20] US-based researchers and IRBs are working on this also with their colleagues in other places, including, when necessary, supporting capacity-building efforts to help those in other countries form and operate their own ethical review boards. No matter where an ethics board or IRB is situated, it applies the same basic ethics to its work. Among IRB professionals, these basic ethical principles are sometimes called the Big Three.

The Big Three—respect for persons, beneficence, and justice—offer instant universal orientation to those concerned about the protection of human subjects within the academic research community. Uniformly in the United States and frequently abroad, we refer to the Belmont Report,[9] the primary guidance document, where one finds the elegant trio. They form the basis of the Common Rule, the US federal regulations. They inspire also the growing wad of checklists and review forms on which investigators and IRBs increasingly depend to survive audits, whether actual or anticipated. They are also being translated into the language of every location where US-based researchers are working with staff and colleagues in conducting research.

The obligations of institutions and IRBs that operate under a federal assurance include ensuring that collaborators, wherever they are in the world, are also complying with these ethical standards. Foreign institutions must also obtain a federal assurance from OHRP if they are conducting human research with US federal funds. To fulfill its obligation to monitor research under its jurisdiction anywhere it takes place,[21] every IRB is required to find a way to use existing infrastructure or develop new infrastructure for communication and to learn about the local research context, observing consent processes and assessing capacity.

Achieving compliant research operations across time zones and languages requires the establishment of solid working relationships between US IRBs and their international partners. This requires not only electronic and digital communication technologies, but also travel and other costs not previously envisioned (something wealthier institutions may be better able to manage than others). Early in 2001, the Office for International Activities was created within OHRP to support the application of the Common Rule and

the principles of respect for persons, beneficence, and justice in international research conducted by US institutions.

CONSCIOUSNESS

The time being *now*, the place *anywhere,* the mission to foster a culture of awareness, US IRBs are being greatly challenged. Not only must they review and approve protocols, monitor behavior, enforce compliance, and guide investigators, but they must do so in a way that ensures that legitimate research can get done—and without unnecessary delays. Despite their virtues, IRBs often cannot respond to submissions fast enough. Delays present obstacles to getting research started (or done at all) and can prevent probable benefits from reaching individuals or society. Investigators are therefore increasingly concerned with the role and function of IRBs and the increasing attention they require.

NIH began requiring a one-time training module for grantees in 2000, but it has since been generally agreed that a one-shot training is not enough. IRBs within the United States are grappling to offer ongoing training, using media such as videos and CD-ROMs and offering classes and workshops where attendees can ask questions, get to know their IRB administrators, and build rapport. Regular workshops led by IRB professionals can be reasonably cost-effective and are adaptable to both basic and specialized content. Employing an administrator to create and deliver a 90-minute PowerPoint presentation might cost an institution several hundred dollars the first time, but only $100 for subsequent presentations of the same slides. Investments in training can potentially save an institution millions of dollars in lost grant funding or lost contributions from donors reacting to shaken trust in the institution.

What are IRBs and federal regulators teaching to inspire investigators and to help make them more comfortable with the process? The importance of maintaining the public trust through compliance with regulations and the Big Three that inspire them: respect for persons, beneficence, and justice. It is reassuring that in the current high-pressure, grant-dependent, immensely complex and fact-driven world of scientific research on human beings, basic ethical principles continue to help make sense of the confusion. The Big Three and a small set of related regulations are being understood and applied at the individual level by researchers in designing better studies, by IRB members in doing their work, and by the public from which human subjects are recruited.

The double challenge posed by the dimensions of place and consciousness is the application of basic ethical principles not only in theory but in practice. In this respect, IRBs are increasingly trying to marshal the resources to conduct site visits to observe consent processes, research procedures, and records. Follow-up with investigators would allow IRBs to give constructive criticism, provide appropriate review, take corrective action, or all three. Such field initiatives could make the IRB real to investigators and its role better known to human subjects, while helping to keep the IRB informed about the realities of the research it reviews. Over time, IRBs may well be able to offer valuable services to investigators through this approach and thereby help to overcome the anxiety and resentment caused by some of the enforcement tasks performed by IRBs.

CONCLUSION

At this writing, there is talk on Capitol Hill about passing legislation consolidating federal oversight of human subjects protections, to strengthen the system by simplifying it.[22] (Currently, 17 federal agencies subscribe to the Common Rule, but several—most notably, the FDA—have their own rules. See the list of 17 codifications at 45 CFR §46, after the table of contents.) Comments are being solicited for modifications to FDA regulations that would require investigators to inform an IRB of previous actions on a protocol by other IRBs, in an effort to avoid "IRB shopping."[23]

Comments are also being sought for changes to the medical privacy rules to ensure a more sensible effect on research and IRBs than the current version projects.[24] There will surely be more contortions in the regulatory landscape as the movement to make compliance manageable continues. Granting agencies will need to give increased attention to the financial resources needed to pay for compliance costs; within the United States, one can ask whether NIH will allow for compliance costs in the budgets of grant applications in the near future.

The key ethical principles, the central moral force of the Belmont Report, and the IRB-based system of review and oversight do not appear to be on the table for renegotiation. On the other hand, effective management of the IRB agenda must remain at the forefront of work in this area. We are involved in developing a quality improvement plan at the Harvard School of Public Health to remedy past weaknesses and to provide a thoroughly compliant program for human research protections. Many improvements have been made and many remain to be made, but years will pass before the measure of success can fairly be taken. The rapidity with which action has been taken, however, cannot be entirely explained by the catalyzing effects of an investigation by OHRP. The public health culture is already receptive to the driving ethics of respect for persons, beneficence, and justice. Public health has, after all, always looked to maximize the social and community benefits of research and clinical interventions.

Speaking with the new regulatory voice, Koski has urged moving "beyond the culture of compliance . . . to a culture of conscience and responsibility."[25] Public health institutions are particularly well positioned in time, place, and consciousness to lead the rest of the research community in the new era of protecting human research subjects. US public health institutions and their IRBs have an opportunity to fulfill a key role in the world if we

can all manage to continue practicing respectful collaboration. ■

About the Authors

Sarah B. Putney is with the Human Subjects Committee and Sofia Gruskin is with the Program on International Health and Human Rights, François-Xavier Bagnoud Center for Health and Human Rights Harvard School of Public Health, Boston, Mass.

Requests for reprints should be sent to Sarah B. Putney, JD, Human Subjects Committee, Harvard School of Public Health, 1613 Tremont St, Boston MA 02120 (email: sputney@hsph.harvard.edu).

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