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Protecting the Rights and Welfare of Human Research Subjects

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When Frank B. Cerra, MD, speaks, he touts a formula that I really like. Cerra, senior vice president for health sciences and dean of the School of Medicine at the University of Minnesota, postulates that "research performance = science + compliance." Compliance, Cerra says, is a cost of doing business (that is, science) that adds value to the ultimate product.

Compliance with federal regulations for the protection of human subjects is an obligation whenever biomedical or behavioral research is conducted or supported by any of 17 U.S. government departments or agencies, or whenever research is subject to regulation by the Food and Drug Administration (FDA). Taking care that no one is hurt in research experiments is an act that benefits both the human study subjects involved and the research enterprise. First, people are kept out of harm's way. Second, public confidence in biomedical and behavioral research is inspired.

Protecting human subjects in research is based on a succession, or chain, of judgments made by people in the context of federal regulations. Thoughtful people, often volunteering large amounts of their time, look at research protocols and weigh risks and potential benefits. There is no computer program for this; there is no generic formula. One size doesn't fit all. This is custom work.

Who is involved in protecting human subjects? The architecture of the current system involves at least half a dozen levels of protection. First, and foremost, there is the interaction between the research volunteer and the research investigator. This is where the informed consent process takes place. There may also be other parties involved, such as nursing, scientific, or medical staff other than the principal investigator. There may be a consent auditor or monitor, or an advocate for the research subject.

Informed consent must be an ongoing, dynamic process, as new information becomes available or is desired. The informed consent document, or form, is one component-the written component-of the informed consent process. Federal regulations specify eight

required elements of information (and six more optional elements of information) that must be conveyed to prospective subjects.

The institutional review board (IRB) is, by federal regulation, to be established at the local level, and has a minimum of five people, including at least one scientist, one non-scientist, and one person not otherwise affiliated with that institution. The non-scientist must be present to achieve a quorum. The local IRB at the research site is the keystone of our system of protection of human subjects. No human-subjects research may be initiated, and no ongoing research may continue, in the absence of an IRB approval. By regulation, 17 federal departments and agencies cannot provide funds for human subjects research unless an IRB approves the protocols for such studies.

IRB review is (1) prospective and (2) continuing review of proposed research by a group of individuals with no formal involvement in the research. Ideally, it is a local review, by individuals who are in the best position to know the resources of the institution, the capabilities and reputations of the investigators and staff, and the prevailing values and ethics of the community and likely subject population.

Once research is under way, the IRB must conduct continuing review of the research, at intervals appropriate to the degree of risk-in any event, at least once per year.

Downstream from the IRB are

- the executive official of the research site (e.g., dean, department chair, chief financial officer);
- the scientific review group at the funding entity (e.g., one of the institutes or centers of the National Institutes of Health); and
- the program and administrative staff (e.g., the executive official) of that funding entity.

Each has the authority to express concerns about human-subjects issues. Exerting oversight of the whole process are the Office for Protection from Research Risks (OPRR) and, when investigational drugs, devices, or biologics are involved, the FDA.

An additional layer of review that may be employed, especially in large studies, is an independent Data and Safety Monitoring Board (DSMB), appointed to oversee and to evaluate the research investigation. DSMBs are usually appointed by, and report to, the funding organization-not the investigators or the institution doing the study. At periodic intervals during the course of the study, the DSMB reviews the accumulated data and makes recommendations on the continuation or modification of the study. A study can be stopped prematurely because of a toxic effect, or because a strong positive effect was seen and it would be unethical to continue with some subjects' not receiving the intervention that has demonstrated benefit. When a study is stopped for such a reason, it is likely to be due to the action of a DSMB.

It is the OPRR's role to make sure that the IRB process works at institutions within OPRR's jurisdiction. This is an active endeavor that depends, to a large extent, on the energy and creativity of institutional leadership. There are four action items at hand for leaders of research institutions: First, all faculty and staff need to receive a memorandum

in which "research" involving "human subjects" is defined. (Those definitions are in federal regulations.) They need the name and phone number of a person to contact with any questions. The memorandum should remind all parties of the institution's obligation to safeguard the rights and welfare of those human research subjects under the institution's auspices.

Second, all faculty and staff who may be involved in human-subjects research need to have in hand a copy of the institution's OPRR-approved assurance of compliance with federal regulations. I would prefer delivery of a hard, paper copy to all, to optimize the chances of the document's being read, but delivery by e-mail or Web posting is an institutional prerogative. All employees need to see and understand the detailed and solemn promises made in the assurance document on their behalf by the institution's high-ranking, signatory official.

Third, institutional leaders should consider sampling IRB records for review, if that is consistent with their respective job descriptions and authorities. IRB records should be the best single integrated index of how an institution is doing with regard to human-subjects compliance.

One IRB record in particular—the written minutes of IRB meetings—should make transparent how the institution is protecting the rights and welfare of human research subjects. IRB minutes are required to show attendance, actions taken, votes, the basis for changes or disapprovals, a summary of controverted issues, and any alterations or waivers of informed consent that the IRB approves. The minutes should show certain findings any time research involving children is approved. If inspection of the minutes of an IRB meeting does not permit determination of precisely how a particular research proposal was handled and discussed at an IRB meeting, and by whom, then the IRB may not actually be doing what it is required to do. A good rule of thumb? If it isn't documented, it wasn't done.

Fourth, institutional leaders should consider surveying IRB members, administrators, and staff to determine their unmet needs for resources. Inadequate institutional support is the number one root cause, in the OPRR's experience, of human-subjects compliance problems. Investment is needed in education, in training, and in the staff or consultants to give support on an ongoing basis. Education is cheap, effective, preventive maintenance for our system of protecting human subjects.

Embedded in the process of protecting human subjects are many issues of substance. For example, an important possibility of harm in research that is often overlooked is the handling of sensitive information. If inappropriately obtained or released, such information can do serious social harm to individuals. Social harms that can result from a breach of confidentiality include such harms as embarrassment (e.g., sexual dysfunction), disruption of family life (e.g., venereal disease), loss of employment (e.g. drug treatment information), and loss of insurance coverage (e.g., HIV status). These harms are real harms. Like physical injury, they can cause pain and suffering. They can ruin people's lives. In conducting research using identifiable medical or other private records, social harms must be given as much consideration as physical harms.

Our enduring and vigorous system of protection of human research subjects is designed

to prevent physical injury, psychological injury, and harm to the dignity of research subjects, as biomedical and behavioral scientists pursue new knowledge for the common good. The OPRR is always interested in improving the system to make research as safe as it possibly can be.

In the final analysis, research investigators, research institutions, and federal regulators are stewards of a trust agreement with the people who are research subjects. For research subjects who are safeguarded by the federal regulations, we have a system in place that (1) minimizes the potential for harm, (2) enables and protects individual, autonomous choice, and (3) promotes the pursuit of new knowledge. By doing so, we protect the rights and welfare of our fellow citizens who make a remarkable contribution to the common good by participating in research studies. We owe them our best effort.

Dr. Ellis is director, Office for Protection from Research Risks, National Institutes of Health, Rockville, Maryland. For additional information about protection of human research subjects, see: <<http://grants.nih.gov/grants/oprr/oprr.htm>>. For an article on a related topic see page 951.

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