Protecting Human Research Subjects: The Past Defines the Future

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The creation of Institutional Review Boards to assure the protection of research subjects came out of terrible research abuses that resulted in the Belmont Report and federal regulations establishing rules for federally funded research and its independent review. The *Common Rule* became widely accepted as the way to oversee human research that is funded by federal agencies, or used in FDA submissions. The Office of Human Research Protections, now under the Secretary of DHHS, created Federalwide Assurances with groups that receive federal funding and others, the vast majority of which have agreed to apply the same ethical rules to all research regardless of funding source. There are controversies over the best methods to protect human research subjects, confusion about how to handle some of the gray areas, increased regulatory burdens, and debates about the adequacy of the IRB system. New exciting directions have evolved and overall, research subjects appear better protected than ever.

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Patients enroll in research trials for many different reasons. Commonly they hope for improvement in their disease, though researchers always tell them this cannot be guaranteed. After all, if we knew the outcome for sure, there would be no need for research. Often they hope to contribute to knowledge that will help others in the future, perhaps because they have seen a friend, relative, or even a stranger suffer or die due to lack of a cure that might come from medical research.

While the reasons for enrolling in a research study may be many, patients expect that their safety will be looked after carefully, and do not expect to be hurt by their participation. But sometimes harm does come to research participants, and researchers must be sure the patient has given a truly informed consent, realizing the potential risks as well as the potential benefits of the research. Everyone in research is responsible for human subject protection. Institutional Review Boards (IRB) are unique in that this is their sole reason for existence.

INFAMOUS RESEARCH BRINGS REGULATIONS

After World War II, there was much publicity and thought given to protecting human research subjects. It was triggered by the Nazi doctors' cruel experiments on people that were exposed in the Nuremberg Military Tribunal. The Nuremberg Code (1947) captured basic principles such as "the voluntary consent of the human subject is absolutely essential," which requires a capacity to consent, freedom from coercion, and comprehension of the risks and benefits involved. It also lists the principles of minimization of risk and harm, a favorable risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the subject to withdraw at any time.

Many thought this was a problem of the Nazi, not American, medical researchers. Yet in 1953, the Clinical Center at the National Institutes of Health (NIH) established a policy for the protection of human subjects. The policy required prior review by NIH and clinical center officials, approval of all non-therapeutic research and all high risk research, and informed consent of research subjects. The Clinical Center policy applied to almost all of the intramural NIH clinical research, but did not reach outside the NIH.

The United States has seen research that unjustifiably caused avoidable and catastrophic harm and violated virtually everyone's ethical standards. The names of infamous studies, such as the Public Health Service's Study of Untreated Syphilis in the Negro Male (the Tuskegee Study) are listed in Table 1. Some of these researchers knew they were actively causing harm to the human subjects, that the risks outweighed the benefits to the subjects, and that the subjects were deceived or had not consented to this with enough information to make an informed decision. The news media picked up the stories and published the details—one example was the *New York Times* headline, *Syphilis victims in U.S. study went untreated for 40 years* (1). A loud public outcry eventually resulted in Congressional hearings, but for many years prior to this there had been complaints about abuse of research subjects.

During the 1962 Congressional hearings about the thalidomide scandal, it was discovered that many patients receiving the drug were not informed that it was an investigational agent, or had not given informed consent. On October 10, 1962, Congress passed the "Drug Amendments of 1962" (P.L. 87-781), and the Food and Drug Administration (FDA) published regulations to implement them on February 7, 1963. Researchers testing investigational new drugs had now to obtain consent, but there were loopholes to the consent requirement. FDA attempted to improve this in August 1966, with new rules modeled after the Nuremberg Code. These FDA regulations had requirements for obtaining written consent and rules for informing subjects that they could be used as control

Table 1. Infamous Research Studies

Dates	Study	Details
Pre-1946	Nuremberg War Crimes Trials	Twenty-three German doctors were charged with crimes against humanity for "performing medical experiments upon concentration camp inmates and other living human subjects, without their consent, in the course of which experiments the defendants committed the murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts."
1932-72	Study of Untreated Syphilis in the Negro Male (Tuskegee Study)	Even after penicillin was available in the 1950s, patients were deceived into thinking they were getting treatment of some kind, and their real diagnosis was not disclosed. The death rate in the infected group was twice that of the control group.
1944-74	Radiation Experiments	Of 18 people given plutonium injections, only one had a documented informed consent. Over 100 prisoners were given non-therapeutic testicular radiation. About 2000 cancer patients were exposed to total body irradiation to help in atomic weapon development.
1950s-61	Thalidomide Studies	Even though FDA did not approve the drug, samples were distributed to US physicians to "research" its safety and efficacy on their patients. By 1961 it was shown to be extremely damaging to the fetus.
1956-72	Willowbrook State School for the Retarded Study	Mentally retarded children were deliberately infected with hepatitis virus.
1960s	Jewish Chronic Disease Hospital	Live cancer cells were injected into 22 senile patients.
1963	Milgram Study	Behavioral study of obedience. Subjects told to give electric shocks to those who missed the right answers to questions. While the electric shocks were not real, great psychological pain was noted in the subjects who thought they were hurting others, as ordered by the investigator. Subjects had been deceived, so no true consent was possible.
1966	Henry Beecher, NEJM 274:1354-60	Twenty-two published medical studies presenting risk to subjects without their knowledge or approval.

subjects, that a placebo could be used, and that, if applicable, alternative therapies exist.

On February 8, 1966, amid a burst of federal funding for medical research mostly through NIH, Surgeon General Stewart issued a memorandum stating that any institution receiving Public Health Service funding, which includes NIH funding, was required to certify to the granting agency that it had reviewed the activity to determine that human subjects would be adequately protected. The NIH developed human subject protection policies to implement this based on its previous intramural policies. The new U.S. Policy set by the Surgeon General forced many institutions to develop committees that evolved into the current IRB system, and to provide assurances that evolved into the current Federalwide Assurance (FWA) of compliance with human subject protection regulations.

The Department of Health Education and Welfare (DHEW) elevated the NIH policies on human subject protection to regulatory status, published them in the Federal Register on May 30, 1974, and noted they would be codified at 45 CFR 46. These agency regulations were an implementation of a new section of the Public Health Service Act (Section 474a) passed by Congress that mandated the development of Institutional Review Boards.

On July 12, 1974, Congress signed the National Research Act into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and requiring approval by an IRB of human subjects research at any institution receiving DHEW funding.

The 11 people on the Commission met monthly for almost four years in addition to an intensive four-day gathering in February 1976 at the Smithsonian Institution's Belmont Conference Center. The *Belmont Report*, issued by the Commission in 1978, is a statement of basic ethical principles and guidelines designed to help resolve ethical problems that surround the conduct of research with human subjects. The *Belmont Report*'s three key ethical principles were respect for persons, beneficence, and justice. These three principles were applied to research by the key applications of informed consent, assessment of risks and benefits, and selection of subjects.

Congress delegates to the federal agencies of the executive branch the task of creating regulations to implement and enforce Congressional laws. Regulations are published chronologically in the Federal

Table 2. Codification of the *Common Rule*

Code	Federal Department or Agency
7 CFR 1c	Department of Agriculture
10 CFR 745	Department of Energy
14 CFR 1230	National Aeronautics and Space Administration
15 CFR 27	Department of Commerce
16 CFR 1028	Consumer Product Safety Commission
22 CFR 225	International Development Cooperation Agency
22 CFR 225	Agency for International Development
24 CFR 60	Department of Housing and Urban Development
28 CFR 46	Department of Justice
32 CFR 219	Department of Defense
34 CFR 97	Department of Education
38 CFR 16	Department of Veterans Affairs
40 CFR 26	Environmental Protection Agency
45 CFR 46	Department of Health and Human Services
45 CFR 690	National Science Foundation
49 CFR 11	Department of Transportation
	Central Intelligence Agency

Register and are later rearranged by subject and agency in the Code of Federal Regulations (CFR). Thus the CFR is administrative law produced by executive branch agencies that are codifying laws passed by Congress. The CFR is divided into titles 1–50, with each title representing a particular topic (e.g., Title 45 is Public Welfare), and each title is divided into parts (e.g., 45 CFR Part 46 is Protection of Human Subjects).

FDA issued 21 CFR 50 (Protection of Human Subjects) on May 30, 1980, and 21 CFR 56 (Institutional Review Boards) on January 27, 1981. These largely paralleled 45 CFR 46 of the Department of Health and Human Services (DHHS, replacing DHEW in 1979/80 as Education was separated out). While DHHS rules apply only to federally funded programs, FDA rules apply to any research study on drugs or devices that are regulated by FDA, regardless of funding.

THE COMMON RULE

Until 1991, different federal agencies used a variety of policies and procedures to protect human research subjects. They all adopted a common Federal Policy as regulation for the protection of human research subjects in research conducted, supported, or otherwise subject to regulation by any of the relevant federal departments and agencies. This became known as the *Common Rule,* which was codified according to agency (Table 2). Additional protections for various vulnerable populations have been adopted by DHHS and are listed in Table 3.

The FDA concurred with the Federal Policy expressed in the *Common Rule*, but did not adopt it in its entirety. Rather, the FDA made selected changes to its IRB and informed consent regulations that correspond to the *Common Rule*. Where a protocol is subject to review under more than one department or agency's regulations, the requirements of each set of regulations must be met.

The *Common Rule* defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge"(2). Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program, which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

The *Common Rule* spells out the criteria an IRB must use in evaluating a study (3):

1. Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design, and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the

Table 3. Special Rules (Subparts of 45 CFR 46)

Subpart	Title	Citation	Date First Published
A	Basic HSS Policy for Protection of Human Research Subjects (the *Common Rule*)	45CFR46 .101-124	May 30, 1974
B	Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women and Human in Vitro Fertilization	45CFR46 .201-207	August 8, 1975
C	Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects	45CFR46 .301-306	November 16, 1978
D	Additional Protections for Children Involved as Subjects in Research	45CFR46 .401-409	March 8, 1983

research (as distinguished from risks and benefits of therapies subjects would receive, even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3. Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research, and the setting in which the research will be conducted, and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.
6. When appropriate, the research plan makes adequate provision for monitoring the data collected, to ensure the safety of subjects.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The *Common Rule* specifies the basic elements of informed consent (4):

1. A statement that the study involves research, an explanation of the purposes of the research, and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. For research involving more than minimal risk, an explanation as to whether any compensation will be provided, and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled.

Additional elements are also listed in the regulations that apply to some studies.

The *Common Rule* is not the only regulation in biomedical research. The FDA has its own regulations that add to the *Common Rule* for FDA regulated products. For example, if a doctor is using a new drug or device in one person just for treatment purposes, it does not meet the *Common Rule* definition of research. However, if the drug or device has not been approved by the FDA for any indication, it does meet the FDA's definition of clinical investigation (5) and must be used only after an IRB has reviewed the "research" and approved it. It may also need additional approvals from the FDA such as an investigational new drug approval (IND) or an investigational device exemption (IDE).

Every study has some risk. Even a simple retrospective chart review study has a risk to privacy. A study must have scientific validity, or there is no benefit that can reasonably be expected to balance its risks. Therefore, the IRB reviews the basic scientific validity of the study, to determine if the benefits outweigh the risks. Consultants can be called in to advise whenever needed.

The IRB is designed by regulation to be sensitive to the local culture and environment. The *Common Rule* requires that each IRB have at least one non-scientist member, and one member not affiliated with the institution. Quorums and simple majority voting are clearly defined in the regulations. If the IRB does not approve a study, it cannot proceed. The institution cannot override the IRB's decision. However, the institution has the right to prevent a study from starting at its site even if it does have IRB approval. The institution's decision to do this may be based on ethics, science, liability concerns, or a simple financial calculation that it will lose too much money on a particular research project.

INSTITUTIONAL ASSURANCES

A loophole in federal regulations for human subject protection has been that the *Common Rule* regulations only apply to federally funded research and FDA test articles. As noted above, the NIH's Office for Protection from Research Risks (OPRR), the precursor of the Office for Human Research Protections (OHRP) now directly under the Secretary of DHHS, developed a system of Assurances that were signed between it and institutions receiving federal research money. These Assurances committed institutions to follow the *Belmont Report* or other ethical norms specified by the institution in all their federally funded research, and required institutions to say yes or no to whether they would voluntarily apply all the same rules to all research conducted at their site. The vast majority said yes. This closed much of the loophole for non-federally funded research.

There are some institutions that do not receive federal research money at all, and have not voluntarily agreed to an Assurance with OHRP. Some institutions have an Assurance but declined to apply the same rules to all their research. For years, Congress has discussed closing this loophole with a law that will apply the *Common Rule* to all research on human subjects regardless of funding. It has not yet happened.

A Federalwide Assurance (FWA) is now replacing the older forms of Assurance (such as the Multiple Project Assurance of MPA). The OHRP website (*http://www.hhs.gov/ohrp/*) has an Assurances link to search for institutions with an FWA. If one does this for Ochsner, one finds our FWA and, in addition, IRBs that Ochsner can rely on for the approval of research studies.

The institution is responsible, under its FWA, for developing, funding, and supporting a human subject protection program. While the IRB may be the major component in such a program, it is not the only aspect. There is a need for research compliance auditors, education of the research staff about human subject protection, and institutional polices that spell out key rules about these areas, misconduct, and conflict of interest. Committees must be available to investigate research misconduct. Institutions may partition these roles in various ways. At Ochsner, the IRB is now separate from the Office of Research Administration, and both are separate from the research compliance auditors. One benefit of this approach is a check and balance system that can improve human subject protection.

CURRENT CONTROVERSIES

There are a number of current controversies and issues in human subject protection. Four of them are briefly discussed here: regulatory burden, adverse events, conflicts of interest, and scientific merit.

One often hears that the increasing regulatory burdens on the local investigators is discouraging them and causing some to give up research as too burdensome. It is true that regulatory burdens are increasing, and that clinicians are busier in their clinical life than ever before. Yet research is critical to developing the best possible patient care. We must find ways to make this livable while we meticulously follow federal regulations. A user-friendly IRB and Office of Research Administration is certainly a good place to begin, and adequate funding for sufficient personnel is important. In today's economic times, this is difficult for many institutions.

Adverse event (AE) reporting is a major challenge. Regulations do not specifically require adverse events be reported to IRBs; rather it is primarily the sponsor's role to monitor AEs and report these to the FDA if a drug or device is involved. But federal regulations do require that "risks to subjects are reasonable in relation to anticipated benefits"(6), provision is made "for monitoring the data collected to ensure the safety of subjects"(7), and there is prompt reporting of "any unanticipated problems involving risks to subjects or others"(8). These have generally been interpreted to mean that IRBs must review at least the AEs that are serious, related and unexpected from the studies they have approved. Sponsors will often want every AE sent to the IRB, yet most are not clinically important (9). While there are AEs that clearly are or are not related to the study drug or device, many of them are in a middle ground where one can only guess about causation. The determination whether an individual had an event that is actively caused by the drug or device is often not possible without broader information, resources, and unblinding. A formal data monitoring committee (DMC) is better at AE analysis to determine implications for changes in, or closure of, a study. DMC reports can substitute for the IRB's review of individual external AEs if these are set up in accord with the October 11, 2005 draft guidance from OHRP.

What is a conflict of interest? How much money from a product or stock ownership can an investigator have and still be allowed to be involved in a trial with that product? Can we independently review a study as long as we are not personally involved with it, or is it a conflict if we are in the same department or even the same institution? These areas will be debated forever, but practical solutions are gradually being developed by institutional and professional society policies. It will never be possible for everyone to be happy with any final conclusion reached.

Can IRBs adequately review the scientific merits of complicated multi-centered trials approved by NIH scientific committees, evaluating the risks and benefits of each arm and comparing them with either standard of care or placebo? By regulation (or at least the current OHRP interpretation of the regulation) they must, and OHRP has recently clarified that this remains the case in spite of protests in national medical journals surrounding the ARDSNet study. How realistic is it to have a local IRB decide that the scientific merits are not worth the risks, in spite of better qualified expert panels from the NIH who come to a different conclusion? These remain open questions even though the current interpretation of the regulations is clear and we try our best to do what is required.

NEW DIRECTIONS

There are some exciting new directions in human subject research protection today that are helping to streamline the process of IRB review.

The National Cancer Institute (NCI) has organized a Central IRB (CIRB) to review all new adult phase 3 oncology studies from the NCI cooperative groups. Each local institution has the option, if it chooses, of participating by adding the CIRB to the local institution's FWA and signing an agreement with it. After the CIRB has approved the study, the local IRB Chair (or delegate) provides a local facilitated review that allows the CIRB to act as the IRB of record, and approves the local template for the informed consent document. This has both theoretical and practical advantages. Expert oncologists who are uninvolved in the local protocol participate in the CIRB, thus eliminating conflict of interest and expertise concerns. On a practical level, this off-loads much work from the local IRB panels, and CIRB, with its greater expertise and resources, can do a better job at future AE evaluations for a study. Given tight local IRB budgets, and the NCI's funding for the CIRB, this appears to be a smart win-win situation to which OHRP has given its blessing.

Sophisticated cutting edge computer software systems for IRB review and research compliance monitoring hold great hope for making the entire process much more user friendly and in compliance with all the federal regulations. Our institution is implementing one of these from Click Commerce (Chicago, Illinois), which allows for sophisticated online applications along with careful tracking mechanisms and detailed reporting and reminder abilities. Unfortunately, these are expensive, have a learning curve, and the financial limitations of many institutions will restrict their use.

Local IRBs are becoming more sophisticated and expanding. This in part is due to FDA/OHRP audits and warning letters in recent years that have closed down research at a few of the country's lead-

ing medical research institutions, and that have cited the lack of an adequate IRB at many others. The FDA and OHRP have made clear in their audits, warnings and determination letters that substandard IRBs will not be tolerated. Institutions have responded by increasing the resources for IRBs, and as a result, a stronger, more experienced IRB system is developing. OHRP's quality improvement program for IRBs (which Ochsner completed a few years ago), and a new organization that is now doing IRB accreditation, are signs of the growing national support system for top quality IRBs. There are also two certifications for IRB staff, the CIM (certified IRB manager) and CIP (certified IRB professional), which can raise the standards for individual knowledge among IRB workers.

The newest direction in protection of human research subjects locally was precipitated by the Katrina disaster. Human Subject Protection Programs should develop a disaster Standard Operating Procedure and have plans for adequate oversight in catastrophic situations when much of the normal infrastructure fails. While we are still developing the details of this post-Katrina, some of the elements might include:

- Assured email, internet, phone, and database access when the normal systems for these fail (integrated into the institution's disaster plans).
- Pre-arranged set-up of an institutional research command center in a non-affected site that can coordinate planning, communications, access to protocols, etc. Investigators, research coordinators, and subjects should know to call into their hot line or make email contact as soon as possible after a catastrophic disaster.
- Established email lists of sponsors and federal officials so the research command center can communicate important information quickly with one click, rather than spending days or weeks locating the right email addresses.
- Development of a list of all research subjects on drug and device trials with contact information so that the research command center can locate them and set them up with needed drug or device follow-up in the critical period when the local Principal Investigator may be evacuated or dead. Perhaps a business card with disaster information and contacts should be given to everyone enrolled in a drug and device trial.

CONCLUSION

Human research subject protection is critical. It is of central importance because we are ethical people, and society has set up regulations to assure minimum ethical standards in protecting subjects. Protecting subjects is also critical to society's research goal, since research subjects will not volunteer if the fear of harm becomes a major issue. Protecting subjects is a joint responsibility of everyone involved in the research enterprise. IRBs have a unique role since this is their reason for existence. While there are theoretical and practical controversies, most IRBs are becoming increasingly sophisticated and more able to provide good oversight of human subject protection, even if it is not a perfect system. The Katrina disaster highlights the need for better planning of research subject protection in catastrophes. We all MUST find a way to promote good research while protecting human subjects, and meticulously following federal regulations.

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