Research in Rural Education, Volume 2, Number 1, Spring, 1983

Preparing Protocols for Institutional Review Boards

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Federal statute and regulations deal extensively with the conduct of research involving human subjects. The Institutional Review Board mechanism was established to comply with these regulations which require peer review and approval of research involving the use of human subjects and funded by the U.S. Department of Health and Human Services. Because of the gravity of the ethical issue involved in such research, the review mechanism has commonly been extended by schools, agencies, universities, and hospitals to include review and approval of all proposals for research, regardless of extent of funding or source of funding. This manuscript is directed at all researchers who utilize human subjects and who therefore are very likely to be in positions which will require them to develop material for presentation to Institutional Review Boards. In it, the composition and process of the IRB are discussed. The basic elements of informed consent and the criteria against which proposals are judged are presented. Finally, a sample protocol format is presented.

The Institutional Review Board (IRB) mechanism for review of research to be funded by the U.S. Department of Health and Human Services is the key element in assuring the protection of human subjects in research. Institutions have commonly extended the province of the IRB to include all proposals for research using human subjects by any member of the institution, regardless of source of funding.

Several forms of research with children in educational settings may be exempt from the federal regulations governing research with human subjects. However, decisions regarding a classification of exempt are normally made by the IRB itself. Therefore, whether a particular research project will be exempt from the regulations or subject to them is unrelated to the obligation of each researcher to be aware of the regulations and to know how to develop a protocol for review by his or her institutional IRB. The text which follows provides an introduction to this process. Additionally, newly published regulations governing research with children are referenced.

Background

The current concern for the protection of human subjects in research has its relatively contemporary roots in the revelation in 1945 that German physicians had carried out experiments using concentration camp prisoners. The subsequent prosecution of Karl Brandt and others by the Nuremberg Military Tribunal led to the development of a set of ten principles which became known as the *Nuremberg Code;*

(1.) The voluntary consent of the human subject is absolutely essential.
(2.) The experiment should be such as to yield fruitful results for the good of society, unprocurable by other means or methods of study and not random and unnecessary in nature.
(3.) The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
(4.) The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
(5.) No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
(6.) The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
(7.) Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury.
(8.) The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
(9.) During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
(10.) During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability or death to the experimental subject.

The *Code* served as the general criterion against which proposals for research with human subjects were judged.

In 1974, the National Commission for the Protection of Human Subjects was established by Public Law 93-348, although broad federal regulations and guidelines had been issued since 1971. Presently, institutions and principal investigators in the United States operate under 45CFR46, from the *Federal Register* of January 26, 1981; March 4, 1983; and March 8, 1983.

The Board

The critical element in implementing the regulations of 45CFR46 is the Institutional Review Board (IRB). The IRB must consist of at least five members. However:

> No IRB may consist entirely of men or entirely of women, or entirely of members of one profession.

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Table 1

Sample Format of a Protocol for Research Involving Human Subjects

Principal Investigator: **Date:**

Assistants: **Agency:**

Title of Project: **New ☐ or Continuation ☐**

Location: **Department:**

Objectives of Project (summarize):

Protocol of Project:

Describe breifly the activity as planned. Include all methods, medications (including dose range, route of administration, name of person responsible for medication), time for single session, number of subjects anticipated, number of sessions, and psychiatric and other methods used to screen subjects. Specify whether males or females are to be used, and age range. Document your experience with this protocol. (Use extra sheet, or back of page if necessary.)

Risks/Benefits:

Identify all risks that might be expected from this project. Describe the benefits to be gained and evaluate the risk/benefit ratio. Are the procedures and activities designed to meet a need or needs of the subjects?

Safety Measures:

Explain how the rights and welfare of the subjects are protected. Specify: safety controls, safeguarding of privacy, discretion in designing questionnaires and scheduling activities, provision for disposal or destruction of materials at the completion of the project, etc. If a physician's attendance is necessary specify the one who will attend.

Informed Consent:

Describe the procedures to be used to obtain informed consent. Attach a copy of the consent form to be used and a summary to be read by or to the subject. Are inducements offered to the subjects?

Cooperating Agency, Individual or Institution:

Identify, and attach a copy of the written agreement.

Continuing Review:

Describe any anticipated circumstances that may require Board review prior to annual review.

Signatures:

Investigator: _____

Each IRB shall include at least one member whose primary concerns are in nonscientific areas; for example: lawyers, ethicists, members of the clergy.

Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

No IRB may have a member participating in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Definitions

Prior to the development or review of proposals, the issue of a definition of the terms research, human subject, and the minimal risk must be addressed. 45CFR46 defines these as follows:

> "Research" means a systematic investigation designated to develop or contribute to generalizable knowledge. Activities which meet this definition constitute "research" for purposes of these regulations, whether or not they are supported or funded under a program which is considered research for other purposes. For example, some "demonstration" and "service" programs may include research activities.
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> "Minimal risk" means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
>
> "Human subjects" means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. "Intervention" includes both physical procedures by which data are gathered (for example, veni-puncture) and manipulations of the subject or the subject's environment that are performed for research purposes. "Interaction" includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information in order for obtaining the information) to constitute research involving human subjects.

The Format of the Protocol

The development of the protocol is critically important to its expeditious treatment by the IRB. Protocols not properly prepared are normally returned to their authors by the IRB Chair for revision. In smaller institutions IRBs commonly meet monthly. A returned protocol, therefore, will mean a one-month delay in action by the IRB on a proposal. The format which appears in Table 1 is similar to many used nationally.

Once the protocol has been prepared and delivered to the IRB, the Chairman will normally assign to it a status of exempt, expedited, or full review. If the protocol is determined by the Chair to be exempt, the author will be so notified and the project may proceed. If the project is assigned expedited status, it will be reviewed. However, the review may be carried out by the Chair or by other IRB members who are appointed to the review team by the Chair. Under the expedited review process, the Chair or review team may approve the project, but may not disapprove it. If they wish to have the project disapproved, they may only recommend such action to the full IRB. If the expedited procedure is used, the full IRB must be informed of the actions which occur in the expedited review of each project.

While institutions may decide for themselves how the determination of exempt status is made, HHS prefers that the Chair of the IRB make that decision. Nationally, institutions commonly follow that practice. 45CFR46 offers the following categories of proposals which may be classified as exempt:

(1.) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2.) Research involving the use or educational tests (cognitive, diagnostic, aptitude, achievement), if information taken from these sources is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(3.) Research involving survey of interview procedures, except where all of the following conditions exist: (i) responses are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the subject's responses, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior, such as illegal conduct, drug use, sexual behavior, or use of alcohol. All research involving survey or interview procedures is exempt, without exception, when the respondents are elected or appointed public officials or candidates for public office.

(4.) Research involving the observation (including observation by participants) of public behavior, except where all of the following conditions exist: (i) observations are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the observations recorded about the individual if they became known outside the research could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior, or use of alcohol.

(5.) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The following are categories of proposals which may be eligible for the expedited review process:

(1.) Collection of: hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth if patient care indicates a need for extraction.

(2.) Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.

(3.) Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves).

(4.) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an eight-week period and no more often than two times per week, from subjects 18 years of age or older and who are in good health and not pregnant.

(5.) Collection of both supra- and subgingival dental plaque and cal-

culus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
(6.) Voice recordings made for research purposes such as investigations of speech defects.
(7.) Moderate exercise by healthy volunteers.
(8.) The study of existing data, documents, records, pathological specimens, or diagnostic specimens.
(9.) Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory or test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.
(10.) Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.

Review of Proposals

In reviewing expedited and full review protocols, the IRB will seek to insure that:

(1.) Risks to subjects are minimized by using the safest procedures consistent with sound research design and whenever appropriate, by using procedures already being performed for diagnostic and treatment purposes;
(2.) Risks to subjects are reasonable in relation to anticipated benefits to subjects and the importance of the knowledge that may reasonably be expected to result. When assessing risk the CRRC will not consider the possible long-range effects of applying knowledge gained in the research;
(3.) Selection of subjects is equitable, taking into account the purposes of the research;
(4.) Informed consent will be sought from each prospective subject or the subject's legally authorized representative;
(5.) Informed consent will be appropriately documented;
(6.) Where appropriate, the research plan makes adequate provision for monitoring the data collected to insure the safety of subjects;
(7.) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data;
(8). Additional safeguards are taken when vulnerable subjects are involved in the research, in order to protect against coercion or undue influence.

In its review, the IRB will be particularly sensitive to assure that the basic elements of informed consent are present in the protocol. 45CFR46 defines these as:

(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 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;
(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.

Although these are the basic elements, more stringent requirements apply for research involving children, fetuses, pregnant women, prisoners, and people in mental institutions. New regulations governing research with children have been published very recently. These regulations were five years in being developed, and call for, among other things, assent by the children themselves, in addition to their parents, for several types of research. Readers are refered to the *Federal Register* of March 8, 1983 for the detailed regulations.

Action by the Committee

Following discussions of the proposal at the meeting of the IRB, the committee may approve the protocol. If it does, however, the project may still be disapproved by the institutional administration on protection of human subjects grounds. However, the institutional administration cannot approve a protocol which has been disapproved by the IRB.