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REGULATION OF THE USE OF HUMAN TISSUES AND BODY FLUIDS AS RESEARCH MATERIALS—CURRENT MODIFICATIONS

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Abstract—The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Commission) has made several recommendations for changes in federal regulations for the protection of human research subjects. Some of these changes will have important and felicitous consequences for biochemical pharmacologists who use human tissues and body fluids as research materials. For most—but not all—proposals to use such materials for research purposes, review at a convened meeting of an Institutional Review Board (IRB) will no longer be required. Similarly, requirements to use consent forms will be curtailed substantially; in some cases it will not even be necessary to negotiate informed consent. The recommendations of the Commission for these policy changes are grounded in recent clarifications of the following concepts: (1) the meaning of risk; (2) the purpose of informed consent; (3) the purpose of consent forms; and (4) the purpose of IRB review.

In the conduct of their research activities, biochemical pharmacologists often use tissues, organs and body fluids obtained from human beings. In the United States, use of such specimens is considered research involving human subjects. Consequently, biochemical pharmacologists commonly find that they are held accountable for compliance with Department of Health, Education, and Welfare (DHEW) regulations designed for the protection of human research subjects [1]. These regulations require, among other things, that investigators prepare detailed accounts of their research proposals and submit them for review by an Institutional Review Board (IRB). The IRB is a committee that is charged with the responsibility of "safeguarding the rights and welfare of human research subjects." The IRB must ". . . determine whether . . . the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks. . . ." The IRB also reviews the plans developed by investigators to negotiate with prospective subjects for informed consent and to document on a consent form that such negotiations have been accomplished satisfactorily.

DHEW regulations require IRB review and documentation of informed consent for all research involving human subjects. These procedural "protections" are required even in cases in which the investigator does not propose to do anything that would jeopardize the rights and welfare of the subjects. For example, in 1975, the National Institutes of Health (NIH) developed a policy requiring the documentation of informed consent to retain for research purposes an organ or fragment thereof removed at either autopsy or surgery, even when these procedures are done in accord with usual and customary medical practice; Holder and Levine [2] have reviewed the destructive consequences of the development of such pointless—and, in this case, legally unjustified—requirements.

In 1974, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Commission) was established by Title II of the National Research Act (P.L. 93-348). The Commission was charged by Congress ". . . to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects . . ." and to make recommendations for guidelines that should be followed to assure that research is conducted in accordance with such principles. The Act further provided a mechanism through which these recommendations were to be translated into federal regulations [3]. In the course of the Commission's deliberations, some important semantic and conceptual clarifications were introduced into the development of regulations designed to protect the rights and welfare of human research subjects. Conceptual elucidations that are of particular importance to clinical pharmacologists have been reviewed elsewhere [4, 5]; they will have a particularly favorable impact on the development of regulations for research involving children [5] and "those institutionalized as mentally infirm" [6].

The purpose of this article is to examine some of the conceptual clarifications recognized by the Commission in its report on IRBs [7]. There will be a particular focus on those that will result in changes in DHEW regulations that are applicable to research conducted by biochemical pharmacologists on specimens obtained from human beings. These concepts include: (1) the meaning of risk; (2) the purpose of informed consent; (3) the purpose of consent forms; and (4) the purpose of IRB review.

Meaning of risk

The widely held belief that all research presents risk

to subjects is reflected in current DHEW regulations [4]. These regulations assign to the IRB the responsibility to determine whether a research proposal will place subjects at risk. Unless the IRB can determine that research will not place subjects at risk, it is required to implement various procedures to assure that the rights and welfare of subjects will be adequately protected, e.g. it must determine that "legally effective informed consent will be obtained." Since, for practical purposes, it is nearly impossible for an IRB to find that human subjects are not at risk, these procedural protections are required for virtually all biomedical research involving human subjects.

In considering the procedural protections required to safeguard the rights and welfare of human research subjects, it is of value to distinguish risk of physical or psychological injury from various other burdens that are more appropriately referred to as inconvenience, discomfort, embarrassment, and so on; Levine [4] has proposed "mere inconvenience" as a general term that may be used to discuss these phenomena. Research presenting mere inconvenience is characterized as presenting no greater risk of consequential injury to the subject than that inherent in his or her particular life situation. The vast majority of research proposals present a burden to the subject that is more appropriately described as mere inconvenience rather than risk of physical or psychological harm. In general, what is asked of prospective subjects is that they give their time (to reside in a clinical research center, to be observed in a laboratory, etc.). Often there is a request to draw some blood or to collect urine or feces. While the withdrawal of venous blood may be momentarily painful and followed by a bruise, no lasting harm is done.

Removal of some normal body fluids may be associated with some risk of substantial physical injury, e.g. fluid from the cerebral ventricles or blood from the coronary sinus. However, it is possible ordinarily to obtain such specimens from individuals who require removal of coronary sinus blood or brain fluid for diagnostic or therapeutic purposes. In these cases, the fact that some of the fluid is removed for research purposes imposes no additional risk or inconvenience on the subject. Similarly, normal tissues are obtained as by-products of medically indicated surgery. It is customary surgical practice to remove a margin of normal tissue around the diseased tissue to assure complete removal of a tumor or of an infection. Thus, it is possible ordinarily to get specimens of most normal tissues without causing even inconvenience to the individual [2].

These considerations are taken into account in the report of the Commission on IRBs [7]. Recommendation 4C requires the IRB to determine that ". . . risks to the subjects are minimized by using the safest procedures consistent with sound research design and, whenever appropriate, by using procedures being performed for diagnostic or treatment purposes. . . ."

Physical and psychological injuries are not the only ones to be considered in developing procedural safeguards for the rights and welfare of human research subjects. Social injuries may be inflicted through violations of privacy or breaches of confidentiality [2]. Research activities which impose on the subject a risk of social injury have two attributes in common.

First, the information to be obtained by the research procedure either will or might be linked to the name of the individual from whom the specimen was removed. If there is no way to link the information to the name of the individual, there is no possibility of putting that individual at risk of social injury.

Second, the proposed research may yield information having diagnostic significance. In this regard, one should be particularly concerned if the presence of the diagnostic information might expose the individual to liability for criminal action (e.g. detection of abuse drugs or alcohol), jeopardize his or her insurance or workmen's compensation status, or create the potential for civil litigation.

In its reports on research involving the various special populations (e.g. prisoners, children, those institutionalized as mentally infirm), the Commission recommends that the need for implementation of various procedural protections for the rights and welfare of research subjects be determined by virtue of whether the proposed research presents risk of injury as distinguished from mere inconvenience [4]. In the recommendations on research involving children [5] and those institutionalized as mentally infirm [6], the Commission stipulates a definition for "minimal risk"; conceptually, minimal risk is equivalent to mere inconvenience. Special justifications are recommended for research proposals which present to the child "minor increments above minimal risk" [5]. Research proposals presenting to children substantial increments above minimal risk must be reviewed by a National Ethical Advisory Board [5].

For proposals to conduct research involving adults who are not members of the special populations [7], the Commission recommends that if there is no consequential risk of physical, psychological or social injury, the needs for various traditional procedural protections may be reduced; in some cases, informed consent need not be documented, and in some others, it need not even be negotiated; for some research proposals, IRB review may be "expedited" (*infra*).

Purpose of informed consent

The requirement for informed consent is derived from the ethical principle of respect for persons [8]. The primary obligation deriving from the principle of respect for persons is that we respect their authority to be self-determining. We are not to touch them or to encroach on their private spaces unless they agree (consent) to such touching or encroachment. A secondary requirement of the principle of respect for persons is that it requires that we protect from harm those who are incapable of protecting themselves.

In its report on IRBs [7], the Commission states: ". . . informed consent is unnecessary, where the subjects' interests are determined to be adequately protected in studies of documents, records or pathological specimens and the importance of the research justifies such invasion of the subjects' privacy . . ." (recommendation 4H). By pathological specimens is meant tissues, organs and body fluids removed for medically indicated reasons. If any additional tissue or fluid is to be removed to serve the purposes of research, informed consent is necessary.

When pathological specimens are used for research purposes, the only way in which the person from whom the specimen was obtained can be harmed is through

breaches of confidentiality (*supra*). The Commission charges the IRB with the responsibility of reviewing such proposals to determine that protections of confidentiality are adequate.

Some persons may—for various reasons—object to having their tissues used for research purposes. In order to show appropriate respect for such objections, the Commission advises in its commentary under recommendation 4H that, when the conduct of research using pathology specimens without explicit consent is anticipated, potential subjects should be notified of this possibility and given an opportunity to provide a general consent or object to such research. To this end, Holder and Levine [2] have recommended that the standard forms used to secure authorization for either surgery or autopsy indicate—when appropriate—that it is customary practice in the institution to retain some specimens for research or teaching purposes before they are destroyed. These forms would alert individuals who wish to object to such use of pathological specimens to do so.

Purpose of the consent form

While the negotiations for informed consent are designed to serve the interests of the research subject, the primary purpose of the consent form is to protect the investigator and the institution against legal liability [8]. The retention of a signed consent form tends to give the advantage to the investigator in any adversary proceeding. Moreover, the availability of signed consent forms in institutional records may lead to violations of privacy and confidentiality.

In recognition of these facts, the Commission recommends [7] that there need be no written documentation of consent if the IRB determines one of two things: (1) the existence of signed consent forms would place subjects at risk, or (2) the research presents no more than minimal risk and involves no procedures for which written consent is normally required (recommendation 4G).

The Commission assigns to the IRB responsibility for reviewing the information that will be presented orally to prospective subjects for purposes of negotiating informed consent. For examples of procedures that might be performed without documentation of informed consent, the reader is referred to the description of activities that might be proposed for "expedited review" by the IRB (*infra*).

Purpose of IRB review

The purpose of IRB review is implicit in the DHEW regulations [1] that describe its composition: "In addition to possessing the professional competence necessary to review specific activities, the committee must be able to ascertain the acceptability of proposals in terms of organizational commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The committee must therefore include persons whose concerns are in these areas." The Commission has recognized [7] that some IRBs may find that certain categories of research recur with some regularity, present no more than minimal risk to subjects, and present no serious ethical issue requiring IRB deliberations. Therefore, the IRB should be permitted to define categories of such research that would receive expedited, rather than full review, thereby enabling it to concentrate its attention on research that presents more serious issues. These categories should be subject to DHEW approval before the expedited procedure can be used (recommendation 5).

Expedited review means that it does not take a convened committee meeting to review a protocol. Rather, one member of the IRB may examine the protocol to see if it fits in the "carefully defined category" and, further, involves no violation of the basic ethical principles governing research involving human subjects. Examples of procedures that might be eligible for expedited review—given adequate assurances of confidentiality—are the following: (1) collection for analysis of excreta and external secretions including sweat, saliva, placenta expelled at delivery, and umbilical cord blood after the cord is clamped at delivery; (2) collection of blood samples by venipuncture, in amounts not exceeding 450 ml in a 6-week period, from subjects 18 years of age and over who are not anemic, pregnant or in a seriously weakened condition; and (3) research using standard protocols or noninvasive procedures generally accepted as presenting no more than minimal risk.

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