

BIOMEDICAL RESEARCH INVOLVING VOLUNTEER SUBJECTS

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I. INTRODUCTION

"The history of medical progress is to a large extent the history of medical experimentation."² Volunteer human subjects are an integral part of any medical research investigation. Testing in humans of a potential drug, device, or vaccine is generally required in order to receive Food and Drug Administration (FDA) licensure. FDA approval and licensure is necessary to make the benefits of the new drug, device or vaccine available to the general public. Human testing is necessary, in part, because the results of animal testing may not be indicative of how a particular drug, device, or vaccine will respond in a human. Testing in human subjects is conducted as part of a *clinical investigation*. A clinical investigation is an experiment that involves a test article (drug, device, or vaccine) and one or more human volunteer that is subject to requirements for submission to the FDA or the results of which are intended to be submitted as part of an application for a research or marketing permit.³

Generally, approval of a potential vaccine by the FDA will only occur if clinical investigation reveals that the test article is both safe and efficacious, meaning that a particular test article will work for its intended purpose. A researcher must produce *substantial evidence* from the clinical investigation that shows that the vaccine (for example) works in humans. The Federal Food, Drug, and Cosmetic Act defines *substantial evidence* as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports to have."⁴

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²G. Annas, *THE RIGHTS OF PATIENTS: THE BASIC ACLU GUIDE TO PATIENT RIGHTS* 141 (Southern Illinois University Press 2d Ed. 1989).

³21 C.F.R. § 50.3(c), Food and Drugs, Protection of Human Subjects, Definitions.

⁴21 U.S.C. § 355(d)(5), New drugs.

II. HISTORICAL EVENTS AND ETHICAL PRINCIPLES

Federal law prohibits the use of human subjects for experimental testing in federal research unless the informed consent of the subject has been obtained.⁵ These federal laws, and others, embody the ethical principles set forth in the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report. The Nuremberg Code is a set of ten ethical principles that developed from the trials of the Nazi doctors in 1947.⁶ The key element of the code focuses on voluntary consent. The code was derived from international law, international customs, basic humanitarian consideration and sensitivities of public conscience.⁷ It now represents international common law and is applied in United States courts.⁸

The Declaration of Helsinki was formulated by the World Medical Association in 1964 as a more specific and workable ethical code for medical personnel.⁹ The most recent revision of this document occurred in 1989. It represents a further evolution of the ethical guidelines to be applied by physicians in clinical and nonclinical biomedical research. Like the Nuremberg Code, The Declaration of Helsinki stresses informed consent while adding a requirement for review of the research study.¹⁰

Finally, the Belmont Report¹¹ resulted from study and deliberations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978). This Commission was established by the National Research Act, P.L. 93-348, to identify the basic ethical principles concerning human subjects that should be applied in the performance of biomedical and behavioral research. The

⁵32 C.F.R. § 219, National Defense, Protection of Human Subjects.

⁶Annas, Mengele's Birthmark: The Nuremberg Code In United States Courts, 7 J. CONTEMP. HEALTH L. & POL'Y 17, 20 (1991).

⁷Annas, *Legal Issues In Medicine: Changing The Consent Rules For Desert Storm*. 326 THE NEW ENGLAND JOURNAL OF MEDICINE 770, 770-773 (1992).

⁸U.S. v. Stanley, 483 U.S. 669 (1987).

⁹Annas, *supra* note 6, at 23.

¹⁰*International Ethical Guidelines for Biomedical Research Involving Human Subjects, Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Geneva, 1993 [hereinafter International].*

¹¹The actual name of the report generated by the Commission is *Ethical Principles and Guidelines on the Protection of Human Subjects of Research*. It can be found at www.tamu.edu/researchandgradstudies/Research/POLICYCOMPLIANCE/HUMANSUBJECTS/belmontrpt.html.

Belmont Report sets forth the guidelines that are incorporated into federal regulations for the protection of human subjects. This guidance is applied in the evaluation of research proposals for federal funding.

Other noteworthy actions include the creation of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical And Behavioral Research (1980-1983), the Advisory Committee on Human Radiation Experiments (1994), and the National Bioethics Advisory Committee (1996). The President's Commission for the Study of Ethical Problems in Medicine and Biomedical And Behavioral Research was created by P.L. 95-622 and required all federal agencies to adopt the Department of Health and Human Services regulations, at 45 C.F.R. 46 (Subpart A), regarding the protection of human subjects (also known as the Common Rule). The deliberations of the Advisory Committee on Human Radiation Experiments resulted in Executive Order 12975 (October 3, 1995), which established the National Bioethics Advisory Committee. The National Bioethics Advisory Committee was established in response to disclosure of human subject abuses in federally supported radiation experiments. The Committee's primary goal was, and still is, to develop clear ethical standards for the protection of human subjects during the conduct of research. The Committee also considers the protection of human subjects in technological applications resulting from that research.

A. RESPECT FOR PERSONS

The consensus within the research and ethics communities is that all research should be conducted in keeping with three basic ethical principles: respect for persons, beneficence, and justice. These principles are considered to have equal moral force although their implementation may be expressed differently in different circumstances. Respect for persons includes respect for the autonomy of the individual. Autonomy is essentially the right of self-determination. Thus, researchers should respect an individual's exercise of self-determination in making decisions about his or her body. The Belmont Report has also emphasized that researchers must respect the individual by giving weight to his or her informed consent to participate in the study and the weighing of the relative risks and benefits of procedures that will be performed. Respect for persons also acknowledges that vulnerable individuals with diminished autonomy should be protected from harm or abuse. All of the ethical guidelines

discussed above focus on autonomy of the subject as a key principle.

B. BENEFICENCE

The concept of beneficence requires that researchers maximize the potential benefits and minimize potential harms to the subject. In other words, the potential risk to the subject must be reasonable in proportion to the anticipated benefits of the research study and the knowledge sought. In addition, the study must be scientifically meritorious, and the researcher must be qualified to conduct the research and competent to protect the subjects from deliberate harm. An individual may choose to participate in a study when death is a probable result. However, the responsibility for the individual must always rest with the medical personnel even though the subject has given his or her consent. Concern for the well being of the individual subject must always outweigh the potential benefit to society as a whole.¹²

C. JUSTICE

Finally, justice requires the equitable distribution of the benefits and burdens of research among the participants and recipients of the benefits of research. Recruitment of subjects should not be limited to specific categories of persons while the general population reaps the benefits of that group's participation. For example, exclusive use of mentally disabled persons as human subjects because of a perception that they are not socially valuable individuals would be improper. Conducting a study with this group of subjects would be permissible if the study seeks to answer some scientifically valid question about mental disability. Treating a specific group differently should be based upon some morally relevant justification or meritorious scientific inquiry.

III. BASIC PRINCIPLES

A. INFORMED CONSENT

Whether to participate in a particular research study is a choice the potential subject must make based on adequate and essential information presented during the process of

¹²Declaration of Helsinki, website, <http://www.bioscience.org/guides/declhels.htm>.

"informed consent." Informed consent requires that sufficient information about the conduct of the research and possible benefits or risks to the subject be presented in such a way that the subject can make a reasoned and informed decision about whether to participate in the research. The standard applied in determining whether there has been informed consent is whether there has been disclosure of all information that a reasonable person would consider material to weighing the potential benefits and risks of participation.¹³ All research utilizing human subjects must comply with this requirement.

In keeping with the ethical principles discussed above, it is important to stress the voluntary nature of the subject's participation throughout the informed consent process. The researcher must avoid any action or statement that could be construed as deceptive, applying undue pressure or influence, or seeking to intimidate the potential subject into signing the consent document. The potential subject must be assured of the ability to withdraw from the study at will and without penalty. If payment or other compensation is to be made for participation, such compensation cannot be so enticing as to be coercive or irresistible to the individual.

In the general research community, informed consent may be obtained orally or in writing. However, written documentation provides the best record of voluntary consent to participation and Army researchers are required to obtain written consent on a DA Form 5303-R, Volunteer Agreement Affidavit, or its equivalent. The consent document must address all of the eight basic elements of informed consent discussed below and may not include any exculpatory language through which subjects are made to waive or appear to waive any legal rights they may have. Furthermore, the consent form should be written in non-medical language that is easily understood by the subject. A translation of the consent form for subjects who do not understand English must also be provided.

It is important to remember that "informed consent" is a continuous process. The informed consent document is not just a piece of paper to be executed at the beginning of a study then filed away and forgotten. The researcher has a continuing obligation to notify the subject of any new information or changed circumstances that may affect his or

¹³*International, supra* note 10, at 15. See also *Canterbury v. Spence*, 464 F.2d 772(D.C. Cir.), *cert. Denied*, 409 U.S. 1064 (1972).

her participation in the study. The researcher's obligation continues even after the study has concluded.¹⁴

B. SELECTED ELEMENTS OF INFORMED CONSENT

There are eight basic elements of informed consent set forth in the Common Rule.¹⁵ At a minimum, these eight elements must become part of the informed consent document but agencies may impose requirements for additional disclosures to the subject. Researchers must provide to the subject a statement that the study involves research, the purpose of the research, the expected duration of the subject's participation, an explanation of the procedures to be performed and identification of any procedures that are experimental. In addition, there must be a description of the reasonably foreseeable risks to the subject of his or her participation as well as benefits anticipated, if any. The subject must also be provided with information about alternative procedures or treatments that might be beneficial to him or her. Confidentiality of medical or research records must be addressed as well as an explanation of compensation to be provided, if any. The subject must also be informed whether no cost medical care will be provided in the case of injury related to the study. Also of extreme importance is the requirement that the subject be made aware that his or her participation is voluntary and that he or she may withdraw from the study at any time without suffering penalties or loss of benefits to which the subject is otherwise entitled. Finally, a point of contact must be provided concerning the subject's participation in the study.

IV. FEDERAL LAW

The body of law governing the use and protection of human subjects in federally funded or conducted research is an amalgam of ethical considerations, international common law, United States statutes and specific regulations promulgated by federal agencies. In 1991, the Department of Defense (DOD), as well as fifteen other federal agencies, adopted Department of Health and Human Services (DHHS) regulations concerning the protection of human subjects in federal research. The adopted

¹⁴Army Regulation 70-25, paragraph 3.2h and Appendix H.

¹⁵32 C.F.R. § 219.116, National Defense, Protection of Human Subjects. The Common Rule applies to all research involving human subjects that is conducted or funded by the Department of Defense.

regulations are referred to as the Common Federal Policy for the Protection of Human Subjects (Common Rule).¹⁶ The DOD adopted Subpart A, 45 C.F.R. § 46, which is implemented at 32 C.F.R. § 219. The DOD did not specifically adopt Subparts B, C, and D of 45 C.F.R. § 46. These subparts address research activities involving fetuses, pregnant women, *in vitro* fertilization (Subpart B), prisoners (Subpart C), and children (Subpart D).

The Common Rule applies to all research funded by the federal government whether intramural or extramural via grants, contracts, cooperative agreements or cooperative research and development agreements. The Common Rule incorporates the principles discussed in the Belmont Report and requires institutional assurances of compliance with federal law, the creation of institutional review boards, and informed consent of the subject to participation in the research study. The DOD currently implements the provisions of the Common Rule with the exception that 10 U.S.C. § 980 imposes additional limitations on DOD research. This law requires that informed consent be obtained in advance from the legal representatives of individuals incapable of providing consent. Such consent is permissible only if the research is intended to benefit the subject. This section would preclude participation in a minimal risk or no risk study when there is no intention to benefit the subject personally. The Common Rule would allow the legal representative to provide consent even if there were no intention to benefit the subject.¹⁷

Army Regulation 70-25, Use of Volunteers as Subjects of Research, is the implementing regulation for the Common Rule as applied by the Army. Several other Army regulations address the use of human subjects during the conduct of clinical investigations.¹⁸ AR 70-25, paragraph 3.1r, sets forth an Army specific requirement to have a medical monitor assigned to each research study that presents more than minimal risks to the subject. The person in charge of the research study (Principal Investigator) generally cannot serve

¹⁶56 Fed. Reg. 28,000 (June 18, 1991).

¹⁷S. de la Vega, Information Paper, 10 U.S.C. 980: Current Law for DOD Medical Research (1997) (available at the Office of the Command Judge Advocate, U.S. Army Medical Research & Materiel Command).

¹⁸AR 40-38, Clinical Investigation Program; AR 40-7, Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances; AR 40-66 Medical Record Administration; OTSG Regulation 15-2.

as the medical monitor unless there is no other physician reasonably available. In this case, approval to serve in both positions must be granted by The Surgeon General.

V. INSTITUTIONAL REVIEW BOARDS (IRBs)

Institutional Review Boards (IRBs) are charged with protecting the rights and welfare of human subjects and to ensure that accepted ethical principles are applied in the conduct of research upon humans. IRBs do this primarily by reviewing research plans (protocols) and serving as biomedical research ethics advisory boards. In the Army system, The Surgeon General (TSG) has the authority to approve the use of human subjects in research studies. The Human Subjects Research Review Board (HSRRB) acts on his behalf¹⁹ in accordance with OTSG Regulation 15-2. The HSRRB has authority to approve, disapprove, or defer approval of the protocol. It may also approve the submitted protocol with modifications or extra protections. In addition, the HSRRB may suspend or terminate an ongoing study.

All Army research studies must be reviewed by an IRB whether the research conducted is intramural or extramural. All protocols must be reviewed prior to beginning the research. Extramural research protocols will be reviewed by the institution conducting the research. Intramural research protocols will generally receive a two-level review. First level reviews of research protocols are conducted by local IRBs within the organization where the researcher works. AR 70-25 refers to these local IRBs as Human Use Committees (HUCs). A second level review is performed by the HSRRB for all protocols presenting greater than minimal risk to the human subject. The HSRRB also serves as the HUC for Army commands that do not have a HUC.

The HUC has an obligation to ensure that the appropriate level of risk has been assigned to the protocol. The risk levels are: exempt, minimal risk, and greater than minimal risk. The FDA regulations defines minimal risk as the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.²⁰

¹⁹OTSG Regulation 15-2, Human Subjects Research Review Board; AR 70-25, paragraph 2.51.

²⁰21 C.F.R. § 50.3k(1).

An analysis of risk should include any risks unique to the study and an estimation of their severity and likelihood of occurrence. The risks presented in the protocol should be compared with risks the subject might encounter in the course of his or her daily activities.

Certain types of studies are exempt from the application of AR 70-25. For example, educational tests in established educational settings and studies involving specimens collected without identifiers are exempt from IRB review. Studies using pre-existing data, documents, specimens of tissue or bodily fluids and lacking any identifiers linking the specimen to the individual source do not require review. However, every aspect of the protocol must fall within an exemption for the protocol to be exempt from review.

In addition to reviewing the informed consent document, the HUC and HSRRB will also review the entire protocol to ensure that the risks to the subjects are minimized and in proportion to the importance of the knowledge to be gained. Selection of subjects will also be reviewed to confirm that the pool of subjects is equitable. The HUC and HSRRB will also review recruitment documents and advertisements to ensure that the study is not misrepresented to potential volunteers. Although the HUC and HSRRB do not perform an independent scientific review, those bodies do consider scientific merit in the risk-benefit analysis when the study presents more than minimal risk to the subjects.

VI. SPECIAL ISSUES

A. WOMEN AND MINORITIES

The FDA and the National Institutes of Health (NIH) guidance encourages diversification in clinical trials unless there is a scientific reason for excluding a certain category of human subjects.²¹ FDA has stated that subjects included in clinical studies should, in general, reflect the population that will receive the drug when it is licensed and marketed. Representatives of both genders should be included in clinical trials in numbers adequate to allow detection of clinically significant gender-related differences in drug responses. In addition, there is usually not sufficient justification for excluding women from trials who are using oral contraceptives or estrogen replacement therapy.²² Similarly, inclusion of minorities in research studies is needed to obtain valid analyses of whether test variables affect members of minority groups differently. With the passage of the National Defense Authorization Act For Fiscal Year 1994, DOD adopted the essential elements of the NIH guidance. The DOD now requires the inclusion of women and minorities in DoD funded or conducted research.²³

The National Academy of Sciences Institute of Medicine has recommended adoption of a policy of presumed inclusion of women of childbearing age and pregnant women in research, with certain exceptions, rather than a policy of presumed exclusion. It is proposed that pregnant women would be excluded from a particular study only when the IRB determines that there is no medical benefit to the subject and that there is significant risk to the fetus. These recommendations are a reaction, in part, to the historical treatment of pregnant women as incompetents in weighing the risks and benefits to participation in research studies. Some commentators have viewed exclusion of pregnant women as disregard for the principles of autonomy, beneficence, and justice.²⁴

B. VULNERABLE POPULATIONS

²¹NIH Revitalization Act of 1993, P.L. 103-43.

²²NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 14508, March 28, 1994.

²³Defense Authorization Act for FY 1994, P.L. 103-160, November 30, 1993. See Conference Report to accompany H.R. 2401, Section 252.

²⁴Rothenberg, *The NIH Inclusion Guidelines: Challenges for the Future*, 18 IRB No. 3 (May-June 1996).

Certain categories of study subjects, such as children, incompetents, and prisoners, constitute "vulnerable" populations for whom special protections are warranted. As a general principle, research studies should utilize subjects that are considered less vulnerable before recruiting more vulnerable populations for participation.

1. Children and Incompetents.

As previously mentioned, research directed to a specific category of subjects must seek to answer a specific scientific question pertaining to that group. For instance, children would be appropriate subjects for research on infectious diseases that afflict mostly children. The DOD regulations specify that the minor's assent (in addition to the legal representative's consent) should be obtained if the minor is capable of understanding the object of the research study and the procedures to be performed.

As an additional protection for minors and incompetents, DOD researchers are bound by the provisions of 10 U.S.C. § 980, Limitation on the Use of Humans As Experimental Subjects. This provision states:

"Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless--(1) the informed consent of the subject is obtained in advance; (2) in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance."

This provision applies only to the DOD and is an additional restriction not contained in the Common Rule. An intention to benefit subjects who cannot give their own consent (e.g., minors, unconscious individuals, incompetents, etc.) must be shown. This intent must be clearly stated in the protocol and consent form. Section 980 provides that the informed consent of an experimental subject must be obtained in advance. When a subject is incapable of providing consent a legal representative may do so, but only when participation in the research is intended to be beneficial to each subject participating in the study.

The determination of whether a particular research activity is intended to be beneficial to the subject is made by the TSG and HSRRB. "Research conducted in accordance with 10 U.S.C.

§ 980 is not legally objectionable merely because it may benefit some subjects more than others, so long as it is clearly intended to provide some reasonable benefit to all subjects."²⁵ An argument can be made that the "intention to benefit" requirement may be satisfied if subjects enrolled in a particular study receive medical treatment or surveillance beyond the usual standard of care. The provisions of section 980 would, however, preclude use of a placebo-controlled group where no expected benefit is to be gained from participation in the study. The prohibitions of section 980 apply even if the study is no risk or minimal risk.²⁶

2. Prisoners.

Although there is no per se prohibition on the use of prisoners as human subjects, studies proposing to utilize prisoners are controversial and should be carefully reviewed. Although DOD has conducted some research involving prisoners, DOD did not specifically adopt Subpart C of the DHHS regulations with the adoption of the Common Rule. However, prisoners of war or detainees will not be used as research subjects.²⁷ Although prisoner populations may be very attractive to researchers because of their standardized living environment and availability for long-term studies, those populations may be susceptible to coercion or unstated pressures to volunteer or continue in a research study.²⁸

3. Soldiers As Subjects.

Soldiers may also be considered a vulnerable population because of the special command authority and restrictions on autonomy imposed by the military environment. In addition, soldiers may have the misperception that they will receive preferential treatment, good performance reports, or other benefits if they volunteer to serve as subjects. Alternatively, they may volunteer because they fear disapproval or retaliation for failure to participate in a command sponsored study. However, participation in any study must be truly voluntary and there are no Uniform Code of Military Justice or administrative actions for declining to participate in or withdrawing from a study.

²⁵Memorandum from Major Dale N. Woodling, U.S. Army OTJAG, Washington, D.C. (1 Sept. 1998)(available at the Office of the Command Judge Advocate, U.S. Army Medical Research & Materiel Command).

²⁶de la Vega, *supra* note 17, at 3.

²⁷AR 70-25, paragraph 3.1(n).

²⁸*International*, *supra* note 10, at 24.

4. Others Who Require Special Protection.

Other groups face similar pressures or misconceptions concerning participation in clinical studies supported or conducted by their organizations. For example, medical and nursing students may feel pressure to volunteer for studies conducted by their teaching hospitals. Persons with advanced terminal diseases may be more vulnerable to recruitment for riskier protocols as a "last hope." Indigents as a group also require special protection as they may have weakened physical and mental conditions, economic disadvantage, and generally, lack any family or community support in decision-making.

C. MEDICAL CARE

It is an Army requirement that the Army research organization or federally funded research organization provide no cost medical care to a subject injured as a proximate result of participation in the research study.²⁹ The informed consent document must state this requirement. Costs of medical care or insurance paid by the federally funded research organization can be negotiated as part of the grant or contract with the Army. The subject should not have to pay any costs associated with the provision of medical care for injuries resulting from the study. The medical care clause should also state that the subject will not receive any injury compensation, only medical care.

D. COMPENSATION RELATED TO PARTICIPATION

It is permissible for research subjects to receive payments or other compensation for participating in a study. Acceptable compensation includes, but is not limited to, reimbursement for transportation costs, other minor or incidental expenses, inconvenience associated with participation, and blood draws. Unacceptable compensation would be that which seems excessive, unwarranted, or appears to be an improper reward to obtain compliance. Compensation that would normally be acceptable may become an unacceptable inducement for a particular person or vulnerable group. Individual situations and cultural considerations must be evaluated in determining whether a particular payment is an improper inducement to participation or at what point a payment might become an improper inducement.

²⁹AR 70-25, paragraph 3.1k. See also Appendix G of that document.

Individuals may receive a reasonable sum, not to exceed \$50.00 for each blood withdrawal under a research study.³⁰ If military subjects are involved in a study and blood is to be drawn, they may be paid only for their blood donation and only up to \$50.00 per draw. Usually, payments are made on a graduated scale based on the amount of blood drawn but may not exceed \$50.00.

E. SPECIMEN DONATION

If blood, tissue, or body product samples will be drawn during the study the subject should be informed as to the procedures by which the specimen will be obtained, the amount of tissue or fluid withdrawn, and its use. Withdrawal of blood, for example, should be described in lay terms such as "two teaspoons worth." Informed consent for obtaining the specimen is always required in autopsies and also when the specimen is linked to a particular person by identifiers, either directly or indirectly.³¹ Consent should be obtained in advance of death from the subject or from the next of kin or legal representative of the deceased person.

If specimens will be obtained in the study for possible future use in another protocol, the informed consent document should include a statement notifying the subject of this possibility. The consent document should also notify the subject that the specimen could potentially have some commercial applicability. If it is indeed anticipated that the samples donated by the volunteer will be used in other studies an additional donation form should be prepared that explicitly donates the specimen to the federal government and relinquishes all right, title, and interest in the specimen.

F. CONFIDENTIALITY AND RECORDKEEPING

Records pertaining to the use of volunteer subjects should include a copy of approved consent documents, a copy of the approved research protocol, minutes of the IRB review, the commander's recommendations, a summary of the research results including any adverse event reporting, and records compiled for the volunteer database.³²

³⁰24 U.S.C. § 30, Payments to donors of blood for persons undergoing treatment at Government expense.

³¹AR 70-25, paragraph 3.2c(2).

³²See AR 70-25, Appendix C-6 for other record requirements.

A volunteer database shall be compiled for all studies involving more than minimal risk to the research subjects. The database will contain personal information about the individual such that a subject's questions about his or her participation in a particular research study can be answered. In addition, the database is necessary to ensure that the research organization can comply with its obligation to adequately warn volunteers of risks and to provide relevant new information as it becomes available. A statement must be included in the consent form notifying the subject that personal information will be collected, the purpose for collection, and duration of time the information will be maintained in the database. The subject must also be notified that representatives of the DOD and FDA may inspect the records of the research in fulfilling their duty to protect human subjects.

The extent to which records will be kept confidential must also be addressed. If the subject is a soldier, notice must be given that complete confidentiality cannot be guaranteed, as certain medical conditions must be reported to the soldier's commander or others. Any system of records must comply with AR 340-21, The Army Privacy Program, and the Privacy Act of 1974.

VII. LIABILITY ISSUES

A. FERES DOCTRINE

The Feres case generally precludes successful suits by service members for personal injury or death incurred that is incident to service.³³ Medical malpractice cases are generally dismissed because medical care in military facilities is considered incident to service, even if the treatment or surgery was elective. A suit brought for personal injury or death resulting from participation in a research study would have certain similarities to a medical malpractice case and would most likely be barred if brought by a service member.

B. TORT LITIGATION

Suits arising from participation in research studies would most likely be filed pursuant to The Federal Tort Claims Act (FTCA). The FTCA waives sovereign immunity to suit in certain

³³Feres v. United States, 340 U.S. 135 (1950).

limited cases.³⁴ The FTCA does not prohibit suits for injury or death resulting from the negligence of government employees in conducting the research study. However, a plaintiff would have to prove that his or her injury is the proximate result of participation in the study and that some duty had been violated.

Litigation would most likely concern issues of informed consent and the adequacy of the informed consent document. Specifically, allegations might assert inadequate disclosure of risks of personal injury or death. Causes of action may also be asserted that research or commercial interest in specimens was not disclosed or that the investigator was influenced in his treatment of the subject by a conflict of interest. There might also be claims resulting from the personal injury or death itself. Although the informed consent document may generate litigation, if drafted properly the document may serve as written evidence that the subject was warned of and acknowledged the risks associated with his or her participation in the study.

Cobbs v. Grant,³⁵ a California medical malpractice case, discussed the evolution of the negligence theory for inadequate disclosure and failure to obtain informed consent. Legal analysis in previous cases employed a battery theory instead of a negligence theory. The Cobbs court concluded that a battery theory should apply only when the procedure implemented is substantially different from the procedure consented to. The court also stated that inadequate disclosure of risks is really a question of the standard of professional conduct. The "patient's dependence upon and trust in his physician for the information upon which he relies during the decisional process raises an obligation in the physician that transcends arms-length transactions."³⁶ The court held that an integral part of the physician's obligation to the patient is a duty of reasonable disclosure of the available choices with respect to proposed therapy and of the dangers inherently and potentially involved in each alternative. Recognizing the difficulty of defining "reasonable," the court went on to state that the scope of a physician's communication to the patient must be measured by the patient's need, and that need is whatever information is material to the decision. Therefore, the test for determining

³⁴The Federal Tort Claims Act, 28 U.S.C § 2671 *et seq.*

³⁵Cobbs v. Grant, 8 Cal.3d 229 (1972).

³⁶*Id* at 242.

whether a risk must be disclosed is its materiality to the patient's decision.³⁷

The standard of disclosure was also addressed in Karp v. Cooley,³⁸ a Texas medical malpractice case involving an experimental heart pump. The plaintiff alleged lack of informed consent because the number of animals in which the device was tested and the results of those tests were not disclosed. The plaintiff also claimed that the risk of injury by the mechanical heart and its experimental nature was never disclosed. The court stated that the standard of disclosure was what a reasonable practitioner of the same school of practice and the same or similar locality would have advised a patient under similar circumstances. The court also stated that "Physicians and surgeons have a duty to make a reasonable disclosure to a patient of risks that are incident to medical diagnosis and treatment...True consent to what happens to one's self is the informed exercise of a choice, and that entails an opportunity to evaluate knowledgeably the options available and the risks attendant upon each."³⁹

Failure to disclose research or commercial interest in specimens or investigator conflicts of interest is another area ripe for litigation. In Moore v. The Regents Of The University of California et al.,⁴⁰ the plaintiff's cells were extracted and used to create a cell line⁴¹ with potentially lucrative commercial applications. The plaintiff was never told that his cells were being extracted for any purpose other than treatment; neither was he told that there might be some economic interest associated with the use of his cells. The court stated that a reasonable person would want to know whether his physician has an economic interest that might affect the physician's professional judgment. The court held that the plaintiff was not required to prove that his cells had potential commercial value at the time they were extracted. The court also held that "a physician who is seeking a patient's consent for a medical procedure must, in order to satisfy his fiduciary duty and to obtain the

³⁷*Id*, citing Canterbury v. Spence, 464 F.2d 772, 780 (1972).

³⁸Karp v. Cooley, 493 F.2d 408 (1974).

³⁹*Id* at 427.

⁴⁰Moore v. The Regents Of The University of California et al., 51 Cal.3d 120 (1990).

⁴¹Cells taken directly from the body have a finite life span. In some cases, cells can be used for an extended time period by developing them into a cell line, which is capable of reproducing indefinitely. See *Id* at footnote 2.

patient's informed consent, disclose personal interests unrelated to the patient's health, whether research or economic, that may affect his medical judgement."⁴² Failure to disclose such interests would give rise to a cause of action for negligence.

VIII. Conclusion

Use of human subjects in research poses unique ethical questions that become more perplexing as biomedical technology increases in complexity and sophistication. The amalgam of ethical considerations, international common law, statutes and regulations protecting volunteer subjects is also becoming more complex. Scientists must seek to understand the necessity for enforcing protections for human subjects while devising new ways to solve scientific conundrums. Ethicists must endeavor to understand the importance of research in advancing knowledge. Regulators must be conscious of the shared objectives and competing concerns of both groups. A balancing of all interests must continue for successful development of new therapeutic drugs, devices and preventative vaccines for the benefit of all.

⁴²*Id.*, at 133.