UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

MAR 28 2005

PERSONNEL AND READINESS

MEMORANDUM FOR PRINCIPAL DEPUTY UNDER SECRETARY (PERSONNEL & READINESS)
ASSISTANT SECRETARY OF DEFENSE (HEALTH AFFAIRS
ASSISTANT SECRETARY OF DEFENSE (RESERVE AFFAIRS)
DEPUTY UNDER SECRETARY OF DEFENSE (PROGRAM INTEGRATION)
DEPUTY UNDER SECRETARY OF DEFENSE (READINESS)
DEPUTY UNDER SECRETARY OF DEFENSE (PLANS)
DEPUTY UNDER SECRETARY OF DEFENSE (MILITARY PERSONNEL POLICY)
DEPUTY UNDER SECRETARY OF DEFENSE (CIVILIAN PERSONNEL POLICY)
DEPUTY UNDER SECRETARY OF DEFENSE (MILITARY COMMUNITY & FAMILY POLICY)
DEPUTY UNDER SECRETARY OF DEFENSE (EQUAL OPPORTUNITY)
DIRECTOR OF THE TRICARE MANAGEMENT ACTIVITY
DIRECTOR OF THE DEFENSE HUMAN RESOURCES ACTIVITY
DIRECTOR OF THE DEPARTMENT OF DEFENSE EDUCATION ACTIVITY
PRESIDENT OF THE UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
DIRECTOR OF THE DEFENSE COMMISSARY AGENCY

SUBJECT: Policy for Protection of Human Subjects in Department of Defense Sponsored Research

REFERENCES: (a) DDR&E memorandum, "Review of DoD Components' Human Subject Research Protection Programs," January 23, 2004
(b) DoD Directive 3216.2, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research," March 25, 2002
(c) Title 10, United States Code, Section 980
(d) Title 32, Code of Federal Regulations, Part 219, "Protection of Human Subjects," current edition

HA POLICY: 05-003

(e) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research report, "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" (Belmont Report)

This memorandum provides policy, assigns responsibility, and describes procedures for formalizing, operating, and maintaining a Protection of Human Subjects Program for those organizational activities under the purview of the Under Secretary of Defense (Personnel and Readiness) (USD(P&R)). It implements applicable provisions of the Department of Defense (DoD) Directive 3216.2 (Reference (b)) and Part 219 of Title 32, Code of Federal Regulations (Reference (d)) and referred to as the "Common Rule."

The Director of Defense Research and Engineering (DDR&E) has overall responsibility for protection of human subjects in research supported by the DoD. Human subject research can apply to any relevant program and is not restricted by budget activity or program title. By Reference (a), DDR&E called upon me to formalize my human research subject protection program for activities under my purview. This memorandum establishes the policy framework for formalizing our program.

All activities under the purview of USD(P&R) will comply with the DoD regulations for the protection of human research subjects, primarily references (b) and (d). All such activities will be guided by the ethical principles regarding all research involving humans as subjects. These principles are set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* ("Belmont Report"), Reference (e). All such activities will accept their responsibilities for protecting the rights and welfare of human subjects of research covered by this policy.

Applicability and Scope.

This memorandum applies to the Office of the USD(P&R) and all activities under the purview of the USD(P&R) that engage in, or may in the future engage in, research involving human subjects to include, but not limited to, the TRICARE Management Activity, the Defense Manpower Data Center, the Department of Defense Education Activity, and the Uniformed Services University of the Health Sciences.

This policy applies to all research involving human subjects and all other undertakings that involve such research even in part, regardless of whether the research is otherwise subject to federal regulation if the research is conducted, sponsored, collaborated in, or supported by a P&R activity; or the research is conducted by or under the direction of any employee or agent of a P&R activity in connection with official duties, or the research is conducted using any property or facility of a P&R activity, or the research involves the use of nonpublic information held by a P&R activity and used

to identify or contact human research subjects or prospective subjects. Research means any systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

This memorandum also applies to other research involving human subjects supported by an entity not within the purview of the USD(P&R) (extramural) through a contract, grant, cooperative agreement, or other arrangement with an activity within the purview of the USD(P&R). The procedures for overseeing P&R-supported research by collaborating entities outside P&R will be specified in P&R's Management Plan.

This policy does not apply to the use of investigational new drugs, biological products, or devices for purposes of force health protection. Such use is not research and is governed by DoD Directive 6200.2.

This policy does not apply to accepted medical practice undertaken for purposes of treatment, not research.

Policy.

All activities under the purview of the USD(P&R) that engage in research involving human subjects, or that may at some future time engage in such research, shall:

- Protect the rights and welfare of human subjects in research supported or conducted by USD(P&R) activities. This protection encompasses basic respect for persons, beneficence, and justice in selection of subjects.

- Ensure that investigators and others directly involved in research are familiar with the Belmont Report (reference (e)), the policies and procedures set out in references (b) through (d), this policy, and any related requirements through initial introductory training before participation in research. Such familiarity initially shall be gained through structured course work provided by instructors with specialized knowledge in those documents and the ethical research standards there embodied. Successful completion of such course work shall be documented. The scope of such training shall be appropriate for each individual's level of involvement and decision-making authority with regard to human subjects research.

- Ensure that investigators and others directly involved in human subject research receive at least annual refresher training in the policies and procedures set out in references (b) through (d), this policy, and any related requirements. Successful completion of such continuing training shall be documented. The scope of such training shall be appropriate for each individual's level of involvement and decision-making authority with regard to human subjects research.

- My authority and responsibility for managing and implementing the component's Human Research Subject Protection Program has been delegated to the Deputy Assistant Secretary of Defense (Force Health Protection and Readiness) (DASD(FHP&R)) as the Component Designated Official. In this role, the DASD(FHP&R) will carry out rigorous and continuous oversight of all aspects of applicable research including but not limited to monitoring and overseeing activities' judgments on whether projects qualify as human subject research, whether research covered by this policy is exempt from Institutional Review Board (IRB) review under the criteria specified in reference (d), and whether adverse outcomes are "significant."

All activities under the purview of the USD(P&R) that do engage in research involving human subjects additionally shall:

- Operate under an assurance of compliance acceptable to the funding agency. Research performed at DoD facilities and funded by DoD shall have a DoD assurance of compliance. Research funded or conducted by the Department of Health and Human Services (HHS) or elements thereof will require an HHS assurance. Research funded or conducted jointly between DoD and HHS elements will require both DoD and HHS assurances.

- Submit assurances of compliance to the appointed official within the office of the USD(P&R) designated to accept assurances indicating that the institutions will strictly follow all principles, policies, and procedures specified in this memorandum and references (b) through (d).

- In general, as required by reference (c), not conduct or use appropriated funds to support research involving a human being as an experimental subject without the prior informed consent of the subject except as authorized by reference (c) and detailed in reference (b).

- Establish an Institutional Review Board (IRB) with appropriate and adequate membership, staff, and support or make arrangements for review of human subjects research by an already established IRB associated with another DoD organization. These IRBs shall review proposed human subject research protocols and plans before the beginning of studies and approve, require modification, or disapprove such protocols and plans. Further, these IRBs will assure continuing review of ongoing studies they have approved not less frequently than once a year.

- Upon recommendation of an IRB, activities under the purview of USD(P&R) will use as appropriate a Data Monitoring Committee (DMC) to regularly review accumulating clinical research data. This may require commitment of support resources for an existing or newly formed DMC. After appropriate analysis of data, the DMC may advise the sponsor and human subject research protection officials regarding the continuing safety of the subjects, as well as the continuing validity of

research, and make recommendations. In accordance with established practice, sponsoring activities will be the final arbiters of whether to engage a DMC and actions to take on DMC recommendations. However, following a DMC's recommendations is the presumptive course of action.

- For research involving more than minimal risk to subjects (as defined in 32 CFR 219.102(i)), an independent medical monitor shall be appointed by name. Medical monitors shall be physicians, dentists, psychologists, nurses, or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. Medical monitors shall be independent of the investigative team and shall possess sufficient educational and professional experience to serve as the subject/patient advocate.

- As provided in reference (b), require and establish additional protections for vulnerable classes of subjects such as fetuses, pregnant women, human in vitro fertilization, prisoners, children, or those judgmentally compromised.

- Require and establish special procedures, consistent with reference (b), for human subject research involving military subjects in a military setting.

Nothing in this policy is intended to contravene the provisions of DoDD 3216.2. If any part of this policy is inconsistent with that Directive, DoDD 3216.2 will prevail.

This policy memorandum is effective immediately.

David S. C. Chu

cc:
Director, Defense Research & Engineering

REFERENCE (a)

DIRECTOR OF DEFENSE RESEARCH AND ENGINEERING
3030 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-3030

JAN 23 2004

MEMORANDUM FOR SECRETARIES OF THE MILITARY DEPARTMENTS
UNDER SECRETARY OF DEFENSE FOR ACQUISITION, TECHNOLOGY AND LOGISTICS
UNDER SECRETARY OF DEFENSE FOR PERSONNEL AND READINESS
DIRECTOR, OPERATIONAL TEST AND EVALUATION
PRESIDENT, UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
DIRECTOR, DEFENSE ADVANCED RESEARCH PROJECTS AGENCY
DIRECTOR, DEFENSE THREAT REDUCTION AGENCY
DIRECTOR, NATIONAL SECURITY AGENCY
DIRECTOR, DEPARTMENT OF DEFENSE EDUCATIONAL ACTIVITY
DEPUTY UNDER SECRETARY OF DEFENSE (ADVANCED SYSTEMS AND CONCEPTS)

SUBJECT: Review of DoD Components' Human Subject Research Protection Programs

I have the responsibility for ensuring DoD's compliance with federal policy for the ethical conduct of RDT&E using human subjects (DoD Directive 3216.2, paragraph 5.1). As Head of a Component, you have been delegated the responsibility to develop, issue, and monitor implementing policies to comply with the Directive (paragraph 5.3). By this memorandum I am initiating a formal process to periodically review and assess compliance with the Directive. In addition, this memorandum terminates all current DoD Assurances as of December 31, 2004 to allow for reissuance following completion of the reviews and assessments.

I have tasked my Director, BioSystems, to conduct oversight visits to all Components that are conducting or sponsoring human - subject RDT&E subject to DoDD 3216.2. I have asked that these visits be conducted between February and May 2004 with a final report delivered to me by the end of July 2004. I hope that the preparation for and exchanges during these visits will strengthen human subject protection programs throughout the DoD. These visits will generate information necessary to reissue authority to relevant DoD organizations to grant DoD "Assurances" so that they can continue to sponsor and conduct RDT&E using human subjects after December 31, 2004.

Dr. Robert Foster, Director, BioSystems, is the Senior Executive responsible to me for these matters and his Action Officer is Patty Decot. If you have any questions, you can reach them through patty.decot@osd.mil or at 703-588-7420. Mrs. Decot will be contacting each Component to schedule the necessary meetings.

Ronald M. Sega

Attachment:
Information Paper

cc:
Office of the General Counsel (ATTN: Mr. John Casciotti)
Assistant Secretary of Defense (Health Affairs)
Deputy Assistant Secretary of Defense Force Health Protection and Readiness
Director of Policy Integration, OUSD(P&R)
Director, Defense Manpower Data Center East (ATTN: Mr. Ken Scheflen)
Acting Director, Defense Sciences Office, DARPA
DTRA (ATTN: LTC Keith Vesely)
USUHS (ATTN: CAPT Robert Bienvenu)
NSA (ATTN: Dr. Julie Sasscer-Bigos)
Surgeon General of the Army
Surgeon General of the Navy
Surgeon General of the Air Force

REFERENCE (b)

Department of Defense

DIRECTIVE

NUMBER 3216.2
March 25, 2002
Certified Current as of December 1, 2003

DDR&E

SUBJECT: Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research

References: (a) DoD Directive 3216.2, "Protection of Human Subjects in DoD-Supported Research, "January 7, 1983 (hereby canceled)
(b) Section 980 of title 10, United States Code
(c) Title 32, Code of Federal Regulations, Part 219, "Protection of Human Subjects," current edition
(d) DoD Directive 6200.2, "Use of Investigational New Drugs for Force Health Protection," August 1, 2000
(e) through (m), see enclosure 1

1. REISSUANCE AND PURPOSE

This Directive:

1.1. Reissues reference (a) to update policies for protecting the rights and welfare of humans as subjects of study in Department of Defense (DoD)-supported research, development, test and evaluation, and other related activities hereafter referred to as "research."

1.2. Implements 10 U.S.C. 980 (reference (b)).

1.3. Supports implementation of 32 CFR Part 219 (reference (c)), referred to as the "Common Rule."

1.4. Establishes other DoD policies for the ethical conduct of research.

2. APPLICABILITY AND SCOPE

This Directive:

2.1. Applies to the Office of the Secretary of Defense, the Military Departments, the Chairman of the Joint Chiefs of Staff, the Combatant Commands, the Office of the Inspector General of the Department of Defense, the Defense Agencies, the DoD Field Activities and all other organizational entities in the Department of Defense (hereafter referred to collectively as "the DoD Components").

2.2. Applies to research involving human subjects, as defined herein, conducted by a DoD Component (i.e., intramural) and other research that is supported by a DoD Component (i.e., extramural) through a contract, grant, cooperative agreement, or other arrangement.

2.3. Does not apply to the use of investigational new drugs, biological products, or devices for purposes of Force Health Protection. Such use is not research and is governed by DoD Directive 6200.2 (reference (d)).

2.4. Does not apply to accepted medical practice, including the use of investigational products in such practice, undertaken for purposes of treatment, not research. Such medical practice is not research and is not subject to this Directive.

3. DEFINITIONS

Terms used in this Directive are as defined in enclosure 2.

4. POLICY

It is the policy of the Department of Defense that:

4.1. Protection of Human Subjects in Research. The rights and welfare of human subjects in research supported or conducted by the DoD Components shall be protected. This protection encompasses basic respect for persons, beneficence, and justice in the selection of subjects.

4.2. Informed Consent. In general, as required by reference (b), no DoD Component may conduct or use appropriated funds to support research involving a human being as an experimental subject without the prior informed consent of the subject.

4.2.1. In the case of research intended to be beneficial to the subject, if the subject lacks capacity, due to age, condition, or other reason, to make a decision regarding consent to participate in the research, prior consent may be provided by a legal representative of the subject. In any such case, the determination that research is intended to be beneficial to the subject must be made by an Institutional Review Board (IRB) under reference (c).

4.2.2. Consistent with 10 U.S.C. 980(b) (reference (b)), the requirement for prior informed consent under paragraph 4.2. or subparagraph 4.2.1. may be waived by the Head of a DoD Component with respect to a specific research project to advance the development of a medical product necessary to the Armed Forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws and regulations, including 21 CFR 50.24 (reference (j)).

4.3. Applicability of Federal Policy for Protection of Human Subjects in Research

4.3.1. The Department of Defense has joined with other Federal Agencies to adopt the "Common Rule" Federal policy for protection of human subjects in research. Reference (c) is the Department of Defense's implementation of the Common Rule. All DoD-supported and -conducted research shall comply with reference (c) and this Directive.

4.3.2. The IRBs of the DoD Components established under reference (c) shall consist of members who are either Federal employees, individuals covered under the Inter-governmental Personnel Act (IPA), or consultants consistent with the requirements established by 5 U.S.C. 3109 (reference (e)).

4.3.3. All human subject research supported or conducted by the Department of Defense shall be conducted under an assurance of compliance acceptable to the funding Agency. Research performed at DoD facilities and funded by the Department of Defense shall have a DoD assurance of compliance. The DoD Components conducting or supporting research must ensure that the investigators are familiar with the Nuremberg Code, the Belmont Report, 32 CFR Part 219 (reference (c)), this Directive, and any related requirements.

4.4. Additional Protections for Certain Categories of Research. In addition to the requirements of reference (c), the following requirements apply to research involving certain subjects or purposes.

4.4.1. Research supported or conducted by the Department of Defense that affects vulnerable classes of subjects shall meet the additional protections of 45 CFR Part 46, Subparts B, C, and D (reference (f)) (e.g., fetuses, pregnant women, human in vitro fertilization, prisoners, or children). For purposes of this paragraph, actions authorizing or requiring any action by an official of the Department of Health and Human Services

(HHS) with respect to any requirements of reference (f) shall be under the authority of the Director, Defense Research and Engineering.

4.4.2. The involvement of prisoners of war as human subjects of research is prohibited.

4.4.3. For research involving more than minimal risk (as defined in 32 CFR 219.102(i), reference (c)) to subjects, an independent medical monitor shall be appointed by name. Medical monitors shall be physicians, dentists, psychologists, nurses, or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. Medical monitors shall be independent of the investigative team and shall possess sufficient educational and professional experience to serve as the subject/patient advocate.

4.4.3.1. Depending on the nature of the study, the medical monitor may be assigned to assess one or more of the following phases of a research project: subject recruitment, subject enrollment, data collection, or data storage and analysis.

4.4.3.2. At the discretion of the IRB, the medical monitor may be assigned to discuss research progress with the principal investigator, interview subjects, consult on individual cases, or evaluate adverse event reports. Medical monitors shall promptly report discrepancies or problems to the IRB. They shall have the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the medical monitor's report.

4.4.4. For research involving more than minimal risk and also involving military personnel, unit officers and noncommissioned officers (NCOs) shall not influence the decisions of their subordinates to participate or not to participate as research subjects. Unit officers and senior NCOs in the chain of command shall not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session. During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an ombudsman not connected in any way with the proposed research or the unit shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate.

4.4.5. Research involving use of human subjects for testing of chemical or biological agents is generally prohibited by 50 U.S.C. 1520a (reference (g)), subject to possible exceptions for research for prophylactic, protective, or other peaceful purposes. Any such research shall comply with reference (g).

4.5. Education and Training on Protection of Human Subjects in Research. Awareness of human subjects protection requirements shall be established for all DoD personnel involved in the conduct, review, or approval of research covered by this Directive.

4.5.1. Awareness activities shall be commensurate with the duties and responsibilities of the participants in the process of protection of human subjects of research, and compatible with Office of Human Research Protections (OHRP) policies.

4.5.2. Research ethics training shall be incorporated into the continuing education program at all DoD Component activities that conduct research involving human subjects.

4.6. Inclusion of Women and Minorities in Clinical Research Projects. The selection of subjects reflecting gender and minority participation as appropriate shall comply with section 252 of Pub. L. 103-160 (reference (h)). The Head of the DoD Component concerned may exercise the waiver authority under this law.

4.7. Fetal Tissue Research. Fetal tissue research supported or conducted by the Department of Defense shall comply with 42 U.S.C. 289g - 289g-2 (reference (i)).

4.8. Research Misconduct. All DoD Components shall establish procedures to monitor and review the ethical conduct of research. The DoD Components that conduct or support research shall ensure that data and data collection are conducted in an ethical manner. In cases in which data are not collected in an appropriate manner, the DoD Component shall determine if the misconduct was intentional or reckless; was an isolated event or part of a pattern; had significant impact on the research record; or had significant impact on other researchers or institutions. The DoD Component shall initiate and carry through on any actions that are necessary to ensure resolution of misconduct findings. All findings of serious research misconduct under this section shall be reported to the Director, Defense Research and Engineering.

4.9. Relationship to Other Requirements. Some activities subject to this Directive may also be subject to regulations of other Federal Agencies, organizations, and non-U.S. entities. Examples include: Food and Drug Administration policies regarding investigational drugs, vaccines, biological products, or devices; multi-agency research; and international research. Activities subject to this Directive and one or more of these other requirements shall comply with all applicable requirements (e.g., references (c) (32 CFR 219.101(g) and (h)), (j), (k), and (l)).

4.10. Non-compliance. Issues related to non-compliance with this Directive by any DoD Component, subordinate, or supported activity shall be referred initially to the next higher management echelon to take deliberate action to resolve. All findings of serious non-compliance under this section shall be reported to the Director, Defense Research and Engineering.

5. RESPONSIBILITIES

5.1. The Director, Defense Research and Engineering, under the Under Secretary of Defense (Acquisition, Technology, and Logistics):

5.1.1. Shall be the single point of contact within the Department of Defense for all matters relating to the Department of Defense's compliance with the "Common Rule" and act as the principal DoD liaison with Agencies outside the Department of Defense on matters pertaining to protection of human subjects in research.

5.1.2. May initiate updates to reference (c) and issue any DoD Instructions or other guidance necessary to implement this Directive. With respect to matters affecting medical research, this shall be done in coordination with the Assistant Secretary of Defense (Health Affairs) (ASD(HA)).

5.1.3. Shall establish a committee to coordinate DoD Component activities in the protection of human subjects. The committee shall be composed of representatives from the DoD Components' human subject protection offices.

5.1.4. Shall exercise the authorities of the Secretary of Defense under reference (c), except for matters not delegable, reserved, or covered by another specific delegation.

5.1.5. Shall establish procedures and standards, consistent with the Federal Policy on Research Misconduct (reference (m)), for the prevention of research misconduct in the Department of Defense.

5.1.6. May grant exceptions to policy under this Directive if justified by special circumstances and consistent with law. Records shall be maintained on exceptions granted under this Directive.

5.2. The Assistant Secretary of Defense for Health Affairs, under the Under Secretary of Defense for Personnel and Readiness shall:

5.2.1. Advise the Director, Defense Research and Engineering on matters related to the involvement of human subjects in research, especially, regarding medical safety, ethics, and standards of professional care and conduct.

5.2.2. Serve as the DoD representative on matters relating to implementation of Food and Drug Administration regulatory requirements (references (j) and (k)).

5.3. The Heads of the DoD Components shall:

5.3.1. Develop, issue, and monitor implementing policies to ensure compliance with this Directive and with any implementing Instructions issued under the authority of this Directive. In research undertakings in which more than one DoD Component is involved, the Heads of the Components shall determine and jointly assign executive responsibility for compliance.

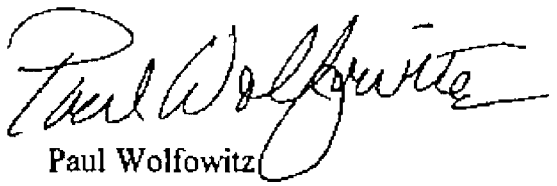
5.3.2. Maintain adequate documentation of DoD-supported or -conducted research involving human subjects and establish procedures for supporting DoD reporting requirements.

5.3.3. Delegate authorities and responsibilities under this Directive to levels of command or authority appropriate to ensure compliance. This shall include procedures for the investigation and resolution of allegations of non-compliance, and may include procedures for headquarters-level administrative review of research. A DoD Component may delegate headquarters-level research review responsibility to another DoD Component for purposes of efficiency and consolidation of functional offices.

5.3.4. With respect to research for which primary involvement is from the Department of Defense, establish the required administrative procedures to protect human subjects from medical expenses (not otherwise provided or reimbursed) that are the direct result of participation in a research project involving more than minimal risk. For this purpose the determination of primary involvement shall be based on consideration of the DoD portion of the total involvement (i.e., funding, personnel, facilities, and all other resources) in the research.

6. EFFECTIVE DATE

This Directive is effective immediately.



Paul Wolfowitz
Deputy Secretary of Defense

Enclosures - 2
E1. References, continued
E2. Definitions

E1. ENCLOSURE 1

REFERENCES, continued

(e) Section 3109 of title 5, United States Code, "Employment of Experts and Consultants, Temporary or Intermittent"
(f) Title 45, Code of Federal Regulations, Part 46, "Protection of Human Subjects," Subparts B, C, and D
(g) Section 1520a of title 50, Unites States Code, "War and National Defense"
(h) Section 2358 note of title 10, United States Code, "National Defense Authorization Act for Fiscal Year 1994," (Public Law 103-160, Sec. 252)
(i) Sections 289g - 289g-2 of title 42, United States Code, "Public Health and Welfare"
(j) Title 21, Code of Federal Regulations, Subchapters A, D, F, and H, "Food and Drug Administration"
(k) Memorandum of Understanding between the Food and Drug Administration and the Department of Defense, "Concerning Investigational Use of Drugs, Antibiotics, Biologicals, and Medical Devices by the Department of Defense," May 1, 1987
(l) DoD Directive 6000.8, "Funding and Administration of Clinical Investigation Program," November 3, 1999
(m) Federal Policy on Research Misconduct, Office of Science and Technology Policy, 65 Federal Register 76260-76264 (December 6, 2000)

E2. ENCLOSURE 2

DEFINITIONS

E2.1.1. Common Rule. The regulation adopted by multiple Federal Agencies for the protection of human subjects in research. The Department of Defense's implementation of the Common Rule is at 32 CFR 219, "Protection of Human Subjects" (reference (c)).

E2.1.2. Research. Any systematic investigation, including research, development, testing, and evaluation (RDT&E), designed to develop or contribute to generalizable knowledge.

E2.1.3. Research Involving a Human Being as an Experimental Subject. An activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction (32 CFR 219.102(f), reference (c)). Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose. This does not include:

E2.1.3.1. Activities carried out for purposes of diagnosis, treatment, or prevention of injury and disease in members of the Armed Forces and other mission essential personnel under Force Health Protection programs of the Department of Defense.

E2.1.3.2. Authorized health and medical activities as part of the reasonable practice of medicine or other health professions.

E2.1.3.3. Monitoring for compliance of individuals and organizations with requirements applicable to military, civilian, or contractor personnel or to organizational units. This includes such activities as drug testing, occupational health and safety monitoring, and security clearance reviews.

E2.1.3.4. Activities exempt under 32 CFR Part 219 (reference (c)).

E2.1.4. Support. Unless otherwise clarified in a specific paragraph of this Directive, this term generally means the provision of funding, personnel, facilities, and all other resources.

REFERENCE (c)

10 USC 980. Limitation On Use Of Humans As Experimental Subjects
(a) 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; or
(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.
(b) The Secretary of Defense may waive the prohibition in this section with respect to a specific research project to advance the development of a medical product necessary to the armed forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws.

REFERENCE (d)

[Code of Federal Regulations]
[Title 32, Volume 2, Parts 191 to 399]
[Revised as of July 1, 2000]
From the U.S. Government Printing Office via GPO Access
[CITE: 32CFR219.101]

[Page 370-371]

TITLE 32--NATIONAL DEFENSE

(CONTINUED)

PART 219--PROTECTION OF HUMAN SUBJECTS--Table of Contents

Sec. 219.**101** To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in Sec. 219.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in Sec. 219.102(e) must be reviewed and approved, in compliance with Sec. 219.**101**, Sec. 219.102, and Sec. 219.107 through Sec. 219.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(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 of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

(ii) Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) The human subjects are elected or appointed public officials or candidates for public office; or

(ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) 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

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a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

(i) Public benefit or service programs;

(ii) Procedures for obtaining benefits or services under those programs;

(iii) Possible changes in or alternatives to those programs or procedures; or

(iv) Possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies,

(i) If wholesome foods without additives are consumed or

(ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. (An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.) In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by

statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the Federal Register or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of Health and Human Services (HHS), and shall also publish them in the Federal Register or in such other manner as provided in department or agency procedures.\1\

\1\ Institutions with HHS-approved assurances on file will abide by provisions of title 45 CFR part 46 subparts A-D. Some of the other Departments and Agencies have incorporated all provisions of title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.**101**(b) do not apply to research involving prisoners, fetuses, pregnant women, or human in vitro fertilization, subparts B and C. The exemption at 45 CFR 46.**101**(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

[56 FR 28012, 28021, June 18, 1991, as amended at 56 FR 29756, June 28, 1991]

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REFERENCE (e)

Department of Health, Education, and Welfare

Office of the Secretary

PROTECTION OF HUMAN SUBJECTS

BELMONT REPORT:

ETHICAL PRINCIPLES AND GUIDELINES

FOR THE PROTECTION OF

HUMAN SUBJECTS OF RESEARCH

Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

Table of Contents

Summary

On July 12, 1974, the National Research Act (Public Law 93348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects, and to develop guidelines, which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: (i) the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, (ii) the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, (iii) appropriate guidelines for the selection of human subjects for participation in such research, and (iv) the nature and definition of informed consent in various research settings.

The *Belmont Report* attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center, supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects.

By publishing the Report in the **Federal Register,** and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of institutional review boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists, who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 780013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the *Belmont Report* does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the *Belmont Report* be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

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THE BELMONT REPORT

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the *Nuremberg Code* was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This Code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied, so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred, partly because both often occur together (as in research designed to evaluate a therapy), and partly because notable departures from standard practice are often called "experimental", when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental" in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage, in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

Research and practice may be carried on together, when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is, that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice.

1. Respect for Persons

Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy, and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals, and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices, while refraining from obstructing their actions, unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part, because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them

as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequences. The extent of protection afforded should depend upon the risk of harm, and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated, and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities, for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. **Beneficence**

Persons are treated in an ethical manner, not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm; and (2) maximize possible benefits, and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person, regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment". Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge, and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined, justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children --even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that, on closer investigation, turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk, without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out, that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. **Justice**

Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved". An injustice occurs, when some benefit to which a person is entitled is denied without good reason, or when some burden is imposed unduly. Another way of conceiving the principle of justice is that, equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property, on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices, such as punishment, taxation and political representation. Until recently, these questions have not generally been associated with scientific research. However, they are foreshadowed, even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries, the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly vagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (*e.g.,* welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected, simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally,

whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them, and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk / benefit assessment, and the selection of subjects of research.

1. **Informed Consent**

   Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided, when adequate standards for informed consent are satisfied.

   While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

   - **Information**

     Most codes of research establish specific items for disclosure, intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, *etc.*

     However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate, since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient, since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be, that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk, and the voluntary nature of participation.

     A special problem of consent arises, where informing subjects of some pertinent

aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research, of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified, only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases, in which disclosure would destroy or invalidate the research, from cases in which disclosure would simply inconvenience the investigator.

- **Comprehension**

  The manner and context, in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration, or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

  Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

  Special provision may need to be made, when comprehension is severely limited --for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (*e.g.,* infants and young children, mentally disabled patients, the terminally ill, and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose, to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected, both by acknowledging their own wishes, and by the use of third parties to protect them from harm.

  The third parties chosen should be those, who are most likely to understand the incompetent subject's situation, and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research, as it proceeds, in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

- **Voluntariness**

  An agreement to participate in research constitutes a valid consent, only if voluntarily

given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another, in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture, in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences, if the subject is especially vulnerable.

Unjustifiable pressures usually occur, when persons in positions of authority or commanding influence --especially where possible sanctions are involved-- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely, where justifiable persuasion ends and undue influence begins. But undue influence would include actions, such as manipulating a person's choice through the controlling influence of a close relative, and threatening to withdraw health services to which an individual would otherwise be entitled.

2. **Assessment of Risks and Benefits**

The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

- **The Nature and Scope of Risks and Benefits**

The requirement that research be justified on the basis of a favorable risk / benefit assessment, bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons.

The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm, and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike "risk", "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk / benefit assessments are concerned with the probabilities and magnitudes of possible harms, and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm, and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests, other than those of the subject, may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects, and also that we be concerned about the loss of the substantial benefits that might be gained from research.

- **The Systematic Assessment of Risks and Benefits**

It is commonly said that benefits and risks must be "balanced", and shown to be "in a favorable ratio". The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished, with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject --or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. **Selection of Subjects**

Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk / benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients, who are in their favor, or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens, and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice, that there is an order of preference in the selection of classes of subjects (*e.g.,* adults before children), and that some classes of potential subjects (*e.g.,* the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators, and treated fairly in the course of research. Thus, injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if institutional review boards are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects, if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized, may continually be sought as research subjects, owing to their ready availability in settings, where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.