



Researcher's Handbook:

Procedures for Researchers
Using Human Subjects

Revised 3 September 2003

Please direct any questions or comments about this Handbook to the IRB Administrator:

Mailing Address:
R&ED Office
801 Leroy Place
Socorro, NM 87801

Email:
red@nmt.edu
Phone:
505-835-5690

Researcher's Handbook for Human Subjects Research at New Mexico Tech
Version 1.0
REV 3 SEPT. 2003

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INTRODUCTION

Purpose of this Handbook

The policies and procedures given in this Handbook are intended to help you comply with federal regulations governing the use and treatment of human research subjects.

New Mexico Tech's Institutional Review Board (IRB) will apply the policies in this Handbook to **all** research involving human subjects that is conducted at, by, or under the auspices of the University, no matter the source (or absence) of funding.

You should read this Handbook carefully to avoid problems in your existing research projects, and to prevent unnecessary delay in obtaining IRB approval for new research projects.

Please be aware that this Handbook is a guide to meeting only the basic requirements for protection of the rights of human research subjects. You are urged to consult with New Mexico Tech's IRB Administrator if you have any questions about whether your research project or classroom demonstration would qualify as "human subjects research," or if you have any questions that are not answered in this Handbook.

Scope of New Mexico Tech's IRB Policy

	<p>All research at New Mexico Tech that involves human subjects MUST be submitted to the IRB for review and approval before such research can be performed. This requirement applies to all human subject research conducted by faculty, staff, or students, on- or off-campus, regardless of the source of funding for the project.</p>
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Federal regulations require that research involving human subjects be reviewed and approved by an Institutional Review Board (IRB) for the Protection of Human Subjects in Research **PRIOR** to initiation of such research.

The IRB must ensure that the rights, welfare, and well being of human participants in research are protected according to the regulations given in the Federal Policy for the Protection of Human Subjects [45 CFR Part 46, also referred to as *The Common Rule*]. These regulations govern human subjects research supported by the Departments of Agriculture, Energy, Commerce, HUD, Justice, Defense, Education, Veterans Affairs, Transportation, and HHS, as well as NSF, NIH, NASA, EPA, AID, Social Security Administration, CIA, and the Consumer Product Safety Commission.

For purposes of New Mexico Tech's IRB Policy, we will use the definition of "research" given in 45 CFR §46.102(d), as follows:

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable

knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

In addition, New Mexico Tech's IRB will use the definition of "human subjects" given in 45 CFR §102.46(f), as follows:

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

- (1) data through intervention or interaction with the individual, or
- (2) identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

In summary: If the project meets the definition of research given above, and if human participants are involved, the research must be submitted for review by New Mexico Tech's IRB.

FREQUENTLY ASKED QUESTIONS

◆ What is human subjects research?

Federal regulations define “human subjects research” as a systematic investigation designed to develop generalizable knowledge, and which involves the collection of data from or about living human beings.

◆ Why does research on human subjects need a special review process?

Federal regulations require that research on human participants be conducted ethically and responsibly. The rights and welfare of human subjects must be adequately protected during all phases of the research project, from inception through data collection, data analysis, writing up of results, and storage of the collected data at the project’s completion.

To help New Mexico Tech fulfill its responsibilities under federal law, the University has established a policy that all human subjects research conducted under its auspices must receive appropriate review and approval by a specially trained Institutional Review Board (IRB).

Even more important than the federal regulations are the ethical responsibilities involved in human subjects research. If you are using human subjects in your research, you have a moral obligation to do no harm to those subjects, to treat those subjects with compassion and respect, and to acknowledge those subjects’ informed decisions regarding participation in your research.

There have been many research projects that were conducted despite being unethical, hazardous, or even cruel. These projects caused severe harm to -- or even killed -- the people who served as their subjects. Some of the more notorious unethical research projects include

- ◆ The Tuskegee Syphilis Study (1932 to 1972) used indigent and poorly educated Black sharecroppers in Alabama to track the natural history of untreated syphilis infections. The participants did not have any meaningful understanding of their illness and did not understand that they were participating in research that was specifically designed to track the course of the disease, rather than cure it.
- ◆ The Willowbrook Hepatitis Study (1950s), in which retarded children institutionalized at the Willowbrook State School in New York were infected with hepatitis to track the transmission and spread of the disease.
- ◆ Atrocities committed upon the inmates of Nazi concentration camps during World War II by Dr. Josef Mengele and others under the guise of medical research.
- ◆ The testing of ionizing radionuclides on children and young adults without their knowledge or consent by the United States Atomic Energy Commission and Department of Energy during the Cold War.

Because of these and other unethical research projects, the federal Department of Health and Human Services drafted a set of regulations to govern the use and treatment of human research participants. The regulations describe procedures that must be followed, but do not provide the

ethical background that researchers should understand and use as a guide during their research projects. To acquaint you with the ethics involved in human subjects research, two important documents that provide the basis for the ethical treatment of human subjects (and which were used to draft the federal regulations) are attached to this handbook. **The Nuremberg Code** (*See Appendix D*) was drafted in response to the Nuremberg War Crime Trials held after World War II. **The Belmont Report** (*See Appendix E*) provides a set of ethical guidelines and guiding principles that should govern Human Subjects Research. The Belmont Report established the three main ethical principles that should govern all human subjects research: Respect for Persons, Justice, and Beneficence.

◆ **Who reviews human subjects research?**

New Mexico Tech's Board of Regents has authorized the IRB to review and approve all human subjects research performed at New Mexico Tech. The IRB is a specially trained committee of Tech researchers, administrators, and at least one non-institutional member and one non-scientist. Some types of research qualify for expedited review, in which the IRB Administrator and one other IRB member review and approve the project. Some projects, such as anonymous questionnaires, may be exempt from mandatory IRB review, but the project must be submitted to the IRB Administrator anyway. Only the IRB Administrator is allowed to determine whether a research project is exempt from mandatory IRB review.

◆ **How do I submit my project to the IRB for review?**

As Principal Investigator, you should fill out an IRB Application Form, attach a complete written description of his/her research project, sign the Application Form in the appropriate spot, and then submit the whole package to Tech's IRB Administrator. In the case of a student-run research project, the student's Research Advisor should sign the Application Form to certify that the project will be monitored. The IRB Application Form is available from the IRB Administrator or via the IRB web site at <http://www.nmt.edu/~red/IRB/>

◆ **When does a research project need to be submitted for review?**

Generally, you should have your research project reviewed by the IRB at the earliest stage possible. Reviewing projects for compliance with federal regulations can be time-consuming. The IRB typically meets once per semester and as needed at other times, as determined by the IRB and/or the IRB Administrator.

New research projects that will involve human subjects can be submitted to the IRB during the proposal routing stage. As Principal Investigator, you should check the "YES" box in the *Human Subjects Research* section on the Proposal Routing Sheet. This will alert the IRB Administrator to your project, and allow him/her to tentatively determine the level of IRB review that may be required for your project. The IRB Administrator will contact you to see if you have completed an IRB Application Form for your project.

Classroom demonstration projects that involve human participants must be written up and given to the IRB Administrator at least two (2) weeks before they are performed. Please note that these demonstrations CANNOT be performed until and unless they have been approved by the IRB.

Existing research projects that use human subjects and which do not have IRB approval must be reviewed and approved as soon as possible. As Principal Investigator for the project, you should contact the IRB Administrator immediately. You will need to fill out an Application Form and provide a written research protocol to allow the IRB Administrator to determine what level of review is required for the existing project. The Administrator will work with you to get the required IRB approval for your research project as quickly as possible.

◆ **How will my project be reviewed? What is the IRB looking for?**

The IRB's review of human subjects research is confined solely to procedures affecting the rights and welfare of human subjects. In its review, the IRB focuses on such issues as risk to subjects, voluntary participation, informed consent, and confidentiality.

◆ **Where can I get assistance with IRB issues?**

The IRB Administrator acts as the liaison between the University community and the IRB. The Administrator, located in the R&ED Office, can assist you in submitting your project for review, or answer any questions that you or your research participants might have regarding the federal regulations.

◆ **What happens if I don't have my project reviewed, or I fail to comply with University policy and Federal regulations regarding use of human subjects in research?**

Principal Investigators and other research staff are subject to any or all of the following consequences if they perform unapproved human subjects research:

- ◆ Mandatory destruction of all research data collected during your project and revocation of your right to conduct research at New Mexico Tech
- ◆ Disciplinary action, including possible termination of your employment at New Mexico Tech
- ◆ Civil or criminal charges could be filed against you and/or New Mexico Tech, if a research subject has an adverse or unexpected reaction due to his/her participation in your project.
- ◆ New Mexico Tech could have ALL of its federal funding revoked. Some universities have experienced this after human participants experienced significant injury or died during non-IRB approved, federally-funded research projects. Federal funding could also be revoked if an audit by federal authorities reveals a pervasive culture of non-compliance with IRB rules.

IN SUMMARY: It is in the best interests of all parties (New Mexico Tech, the Principal Investigator, and the research participant) to have all research projects involving human subjects approved by the IRB. Such review helps to ensure that the ethical principles of respect for persons, beneficence, and justice have been honored. Human subjects' participation in research should be protected as a matter of ethics, not merely as a matter of "compliance" with New Mexico Tech or federal rules.

THE ROLE AND RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR

As a Principal Investigator (PI), you have five primary responsibilities in protecting the rights and welfare of human research subjects who participate in your research project(s).

◆ Obtaining training and certification for all research personnel on project

In order to conduct research involving human subjects, you and any research staff who will work directly with the human subjects in your project must complete a training course on Human Subjects Use. For student-run research projects, the Research Advisor or faculty/staff researchers who supervise the student investigator are responsible for being certified and ensuring that appropriate procedures are used.

You must take a refresher course on the ethical use of human research participants at least every three years in order to remain eligible to perform human subjects research.

The current training course that you should use is an online tutorial provided by the National Institutes of Health. This tutorial, entitled "Human Participant Protections: Education for Research Teams," is located at the following URL:

http://cme.cancer.gov/c01/nih_intro_01.htm

This tutorial will require approximately two hours to complete. Once you have completed this online tutorial, you should print out your completion certificate and bring it to the IRB Administrator in the R&ED Office. You will then be given a numbered completion certificate from New Mexico Tech that permits you to perform human subjects research.

	<p>Under the policy approved by the New Mexico Tech Board of Regents, if you submit an IRB Application Form to the IRB to have your project reviewed, you must take the required training course. The IRB will not approve your project until you have completed the required training.</p>
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◆ Submitting proposed human subjects research to the IRB for review and approval

If your research project meets both criteria for IRB review (i.e., it is considered "research" as defined in the regulations, and it involves human subjects), you must seek approval from the IRB before commencing the research project.

You should obtain an IRB Application Form and fill in all required fields on the Form. The Application Form can be downloaded from the R&ED web site at <http://www.nmt.edu/~red/IRB/> or obtained from the IRB Administrator.

Make sure you attach a complete written description of your research project to the Application Form. You must describe how you will protect the rights and welfare of prospective subjects and ensure that pertinent law and regulations are observed. Samples of all proposed informed consent documents must also be included with the written description. The whole application package must be submitted to the IRB Administrator in the R&ED Office.

If you are not sure whether your research project will involve human subjects, you should seek assistance from the IRB Administrator in making this determination [45 CFR §101(b)(1)-(6), §118, and §119].

◆ **Obtaining IRB permission prior to any changes in research project**

You **MUST** seek review and approval from the IRB before making any changes to a previously-approved research project, except when necessary to eliminate apparent immediate hazards to the research participants.

◆ **Reporting progress of research project to the IRB on a regular basis**

As Principal Investigator, you must report the progress of your research project to the IRB and/or appropriate institutional officials as often as and in the manner prescribed by the IRB but no less than once per year [45 CFR §109(e)].

◆ **Soliciting informed consent from each potential subject involved in the research project**

	<p>You cannot use a human being as a subject in research covered by this policy unless you have obtained the legally effective informed consent of the subject or the subject's legally authorized representative.</p>
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According to the NIH online training tutorial:

Informed consent in research means more than simply obtaining the signature of the potential research participant. It is a process that involves conveying accurate and relevant information about the study and its purpose; disclosing known risks, benefits, alternatives, and procedures; answering questions; and enabling the potential participant to make an informed decision about whether to participate.

The federal regulations at 45 CFR 46.116(a) mandate the inclusion of eight basic elements in Informed Consent. Six additional elements may also be required, depending upon the nature of the research project.

Required Element #1: Research Statement

Informed consent information must include the following:

1. A statement that the study involves research;
2. An explanation of the purposes of the research
3. An explanation of the expected duration of the subjects' participation
4. A description of what procedures will be followed.
5. Identification of any procedures that are experimental.

Required Element #2: Reasonably Foreseeable Risks or Discomforts

Informed consent information must describe any reasonably foreseeable risks or discomforts associated with the research. Risks should be listed in descending order of probability and magnitude (for example: risk of death –even if remote – should be listed before risks associated with blood draw).

Required Element #3: Reasonably Expected Benefits to Subjects or Others

Informed consent information must describe any benefits to the subject or to others that may reasonably be expected from the research. However, care must be taken not to overstate the benefits and create an undue influence on the subjects. Payment for subject's participation in a research project is NOT to be considered as a benefit of the research.

Required Element #4: Appropriate Alternatives

Informed consent information must include a disclosure of any appropriate alternative procedures or courses of treatment that may be advantageous to the subject. Enough detail must be presented so that the subject can understand and appreciate the nature of any alternatives.

Required Element #5: Extent of Confidentiality

Informed consent information must describe the extent to which confidentiality of records identifying the subject will be maintained (or not maintained). Research often poses the risk of loss of confidentiality to subjects who participate. Many persons who would not otherwise have access to identifiable, private information about the subject may be involved in the research process. Consent information should describe any procedures that the research team will use to protect subjects' private records. In some research, loss of privacy may be the greatest risk of participation.

Required Element #6: Compensation or Treatment for Injury

Informed consent information for research involving more than Minimal Risk must include explanations regarding:

1. Whether any compensation is available if injury occurs.
2. In accordance with Federal law, a statement that subjects shall receive medical care and treatment for injuries suffered as a result of participating in a research program, and whether any medical treatments are available if injury occurs.
3. A description of any such compensation or treatments, or where more information about them is available.
4. A description of any applicable state law.

Required Element #7: Contact Information

Informed consent information must include details, including telephone numbers, about whom to contact for three specific situations:

1. For answers to questions about the research. The Principal Investigator and other members of the research team are appropriate contacts for this information.
2. For answers to questions about subjects' rights. The IRB Administrator is the appropriate contact for this information, so the following contact information should be included:

IRB Administrator
c/o Research & Economic Development Office
New Mexico Tech
801 Leroy Place
Socorro, NM 87801
Phone: 505-835-5690

3. In the event a research-related injury occurs. The Principal Investigator and other members of the research team may serve as the appropriate contact for this information.

Required Element #8: Voluntary Participation Statement

Informed consent information must contain clear statements of the following:

1. Participation in research is voluntary.
2. Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.
3. The subject may discontinue his/her participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional Elements Required Where Appropriate

Where appropriate, the regulations require that one or more of the following six additional elements must be included in the informed consent information:

1. Unforeseeable Risks to Subjects, Embryos, or Fetuses. Some research involves particular procedures or interventions that may result in unforeseeable risks to subjects, to the embryo, or the fetus (if the subject is or may become pregnant). For research of such a nature, the informed consent information must warn subjects that some risks are currently not known or not foreseeable.

2. Investigator-Initiated Termination of Participation. There may be instances that would require investigators to terminate the participation of particular subjects (e.g., subject non-compliance with research, subject not benefiting from research). The informed consent information must specify these circumstances.
3. Additional Costs. If subjects must bear any additional costs (transportation, time away from work, health costs, etc.), these must be disclosed in the informed consent information.
4. Early Withdrawal/Procedures for Termination. Subjects have the right to withdraw from the research. However, some studies involve medications or procedures that would be dangerous for subjects to discontinue abruptly. For studies of this nature, the informed consent information must provide subjects with knowledge of the consequences affecting a decision to withdraw. In addition, if there are procedures regarding how to withdraw safely from the research, these must also be described. It is not appropriate for research staff to administer any additional research-oriented questionnaires or interventions that do not affect the safety of subjects who have decided to withdraw.
5. Significant New Findings. During the course of research, significant new knowledge or findings under study may develop. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the informed consent information must detail the procedures for contacting subjects regarding this new information and for affirming their continued participation.
6. Approximate Number of Subjects. For certain types of research, the informed consent information should disclose the approximate number of subjects to be enrolled.

CONSEQUENCES OF NON-COMPLIANCE WITH THIS POLICY

According to the OHRP, research investigators are the most frequent source of non-compliance with human subjects regulations. The most common lapses in investigator compliance include unreported changes in research protocols, misuses or non-use of the informed consent document, and failure to obtain IRB approval prior to commencement of research. Problems such as these are often caused by lack of communication and may in fact be unintentional. However, regardless of investigator intent, unapproved human subjects research places those subjects at an unacceptable risk.

Primary Investigators and other research staff should be aware that they are subject to any or all of the following consequences if they perform unapproved human subjects research:

◆ **Mandatory destruction of all research data and revocation of the right to conduct research**

The New Mexico Tech IRB or the federal government *may* require that all research data that was collected before IRB approval of the project (or collected after IRB approval has been rescinded) be destroyed. Federal agencies can and have required that all research at a given university be halted while individual research projects are re-reviewed. Failure to comply with human research participant rules can cause a researcher's right to conduct research to be withdrawn.

◆ **Revocation of ALL federal funding to New Mexico Tech**

Another consequence that can result from performing human subjects research that has NOT been reviewed by New Mexico Tech's IRB could include revocation of all of New Mexico Tech's federal funding, regardless of whether the research in question is using federal funding or funding from a different, non-federal source.

◆ **Criminal or Civil Charges**

Additionally, if a human subject experiences unanticipated negative effects from participating in an unapproved research project, criminal and/or civil charges could be filed against either the researcher or New Mexico Tech or both.

◆ **Disciplinary Action, Including Possible Termination of Employment**

	<p>Researchers who fail to comply with New Mexico Tech's IRB policies and procedures will be subject to appropriate disciplinary action which could range from suspension of the research project to termination of employment at New Mexico Tech, depending upon the severity of the problem.</p>
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◆ How Allegations of Non-Compliance will be handled

Whenever an unapproved research project using human subjects is discovered, the IRB and New Mexico Tech officials will act immediately to halt the research project. The full membership of the IRB will then perform an investigation to determine which regulatory or institutional human subject protection requirements the unauthorized research project may have breached.

The results of this investigation, along with any suspensions, terminations of research, and noncompliance findings will be reported in writing to the Vice President for Research and the funding federal department or agency within 10 business days of determination of the Full Board. Serious violations of the federal regulations will be reported in writing to the Office for Human Research Protections (OHRP) as well as any applicable regulatory body, if necessary.

IN SUMMARY: It is in the best interests of all parties (New Mexico Tech, the Principal Investigator, and the research participant) to have all research projects involving human subjects approved by the IRB. Such review helps to ensure that the ethical principles of respect for persons, beneficence, and justice have been honored. Human subjects' participation in research should be protected as a matter of ethics, not merely as a matter of "compliance" with New Mexico Tech or federal rules.

PROCEDURES FOR PLANNING A RESEARCH PROJECT AND APPLYING FOR IRB APPROVAL

When you are going to conduct any research project involving human subjects, you should contact the IRB Administrator as early in the project as possible. Aspects of a project that may be problematic can be discussed and alternative procedures suggested.

The following checklist may prove helpful when planning a research project:

◆ Have you and all research staff successfully completed an approved training course in the use of Human Subjects?

The OHRP requires that all investigators using human subjects in research receive formal training in the ethical and legal requirements involved in such research.

New Mexico Tech researchers should use a special online tutorial provided by the National Institutes of Health. This tutorial, entitled "Human Participant Protections: Education for Research Teams," is located at the following URL:

http://cme.cancer.gov/c01/nih_intro_01.htm

This tutorial does not require any browser plugins. The website recommends using Netscape Navigator v4.0 or higher, or Internet Explorer v5.0 or higher to view and complete the tutorial.

This tutorial requires approximately 2 to 3 hours to complete. The tutorial is divided into sections, with a self-test at the end of each section. At the completion of this tutorial, you will receive an online completion certificate stating your name, the date of completion, and the course objectives. You should print out the online certificate for your files, and provide a copy to the IRB Administrator. You will be given a numbered completion certificate from the New Mexico Tech IRB that will allow you to perform human subjects research.

◆ Is your project considered "research" under federal regulations?

Research is defined in the Federal regulations as *"systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."*

In general, research that involves data gathered solely for internal, on-going campus use would not need to be reviewed (e.g., course evaluations or institutional research). If, however, the results of your research will be **disseminated in any way**, then the research must receive IRB approval. If you do not plan to disseminate the data when it is gathered, but the possibility of future dissemination exists, you should submit the project to the IRB for review and approval before initiating the research.

◆ Does your project involve human subjects?

A human subject is defined in the federal regulations as *"a living individual about whom an investigator (whether professional or student) conducting research obtains 1) data through intervention or interaction with the individual or 2) identifiable private information."* ["Identifiable Private Information" includes addresses, identification numbers, demographic information, etc. that may be used to link specific information or data back to an individual.]

	<p>As Principal Investigator, you are responsible for making the initial determination as to whether your research project should be considered human subjects research. This determination should be based on the definition given above, and the decision flow chart shown in Figure 1 below. If you aren't sure whether your project needs IRB review, please consult with the IRB Administrator for advice on this question. Final authority for making this determination rests with the IRB or its designee.</p>
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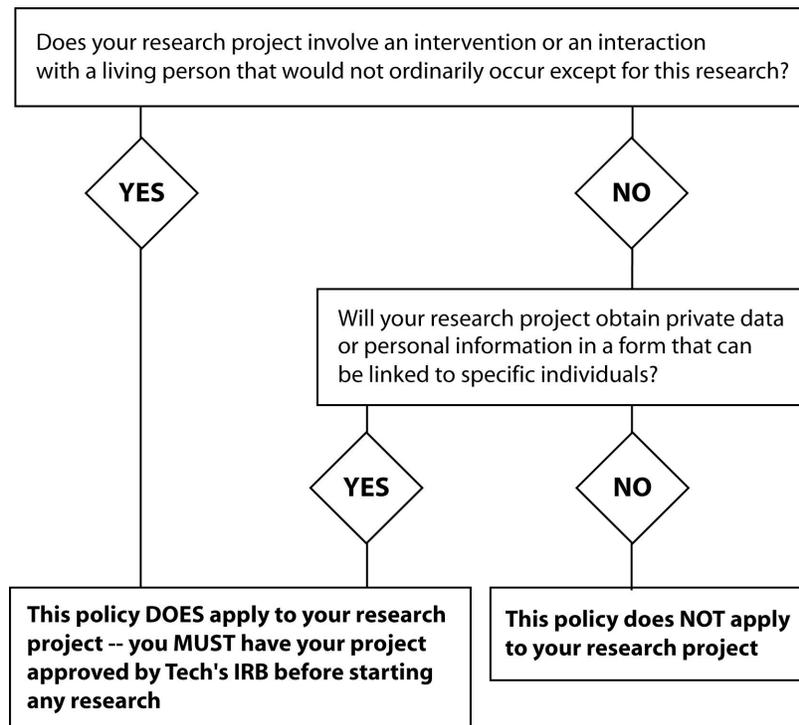


Figure 1: Decision Flow Chart for determining whether a research project involves Human Subjects

◆ If you are using existing or archival data, do you still need to obtain IRB approval?

Yes, if the study meets the definitions of both “human subjects” and “research” discussed above. The decision flow chart given in **Figure 2** below may help you determine if your research project needs IRB review and approval. This type of project may be eligible for administrative review if no identifiable private information or data exist in the data set.

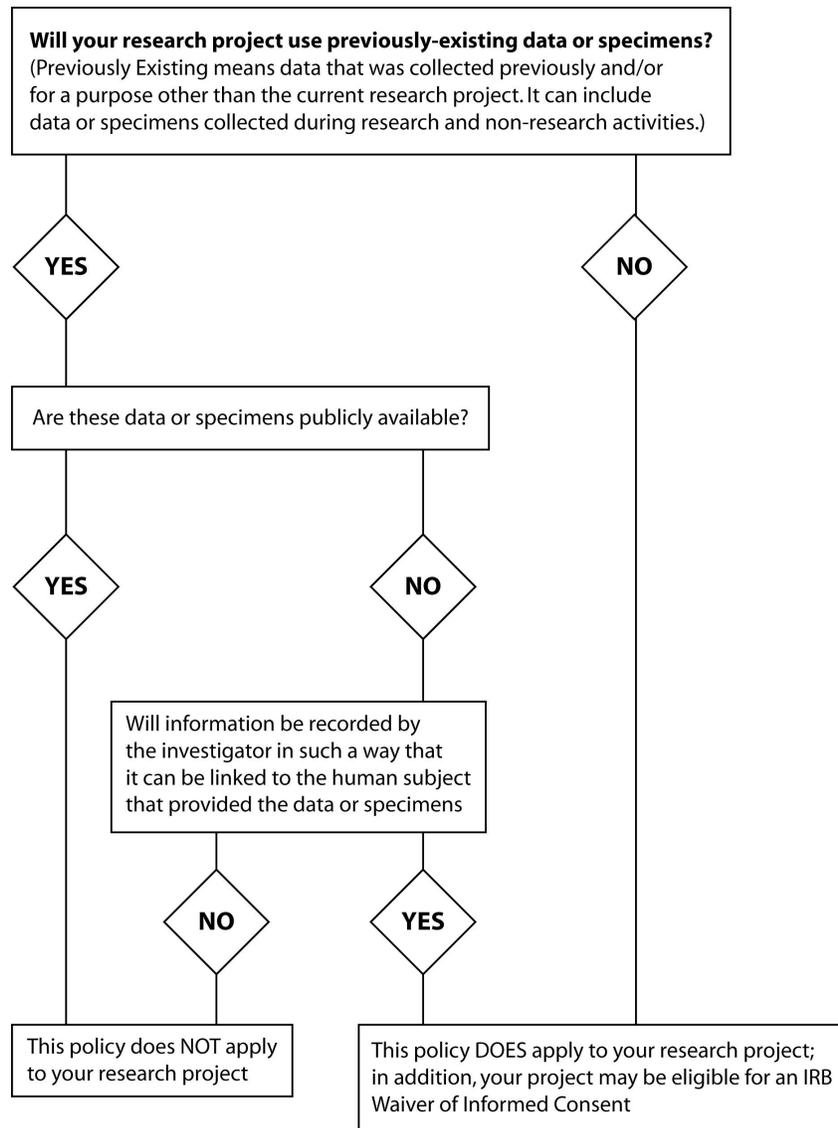


Figure 2: Decision Flow Chart for determining whether a research project involving archived or existing data will require IRB review or qualify for waiver of informed consent.

Special Policy for Educational Records

If the existing data could be considered “educational records,” another set of federal regulations called the Family Educational Rights Privacy Act (FERPA) come into play. These regulations apply to identifiable records to which PIs may have access in the course of their daily duties (e.g., an instructor typically has access to the grades of all students enrolled in his/her class. Grade reports and certain other types of personal information fall under the FERPA regulations.) **IRB approval must be obtained BEFORE using this type of data in a research project.**

◆ Your project meets both of the criteria for “research” and “human subjects” listed above. Now what?

Any research project that involves human subjects must be submitted to the IRB for review. You should obtain an IRB Application Form, fill it in and sign it, attach a complete written description of your research project, and then submit the whole package to Tech’s IRB Administrator. The IRB Application Form is available from the IRB Administrator or via the IRB web site at <http://www.nmt.edu/~red/IRB/>

Please make sure your Application Form is readable. Any illegible Application Form will be returned to the Principal Investigator without being reviewed.

Please also make sure that you sign the Application Form. In the case of student research projects, the student’s Research Advisor for the project should sign the Application Form.

Additional Materials that should accompany the Application Form -- The following items, where appropriate, must be included with the Human Subjects Use Application Form:

- Complete written description of methodology to be used in the research project
- Copies of any Consent Forms and if applicable, Assent Forms (or scripts if verbal consent procedures will be used)
- Copies of all questionnaires/surveys/interview questions
- Copies of any recruitment materials (i.e. anything you will use to recruit subjects including press releases and flyers)
- School district/organization permission (required on appropriate letterhead) to conduct research (These can be submitted following IRB review, but final approval will be pending receipt)

◆ How do I obtain “Informed Consent” from the participants in my research project?

Informed consent is not a single event, nor merely a form to be signed. It is an educational process that occurs between the PI and the research subject.

In order for a participant’s consent to be valid, it should be based on the following critical elements:

- ◆ The participant must be **COMPETENT** to begin the informed consent process. If the participant is not competent because of age, illness, incapacity, or any other reason, special provisions apply, or the participant may not be included in the research.
- ◆ The research team must **DISCLOSE** all relevant information to the potential participant. The information must be sufficient to allow the potential participant to decide whether to participate. It is generally accepted that the potential participant must be given the following information: the purpose of the study; nature of the procedure; reasonable alternatives to the proposed intervention; and risks, benefits, and uncertainties of each possible intervention.

- ◆ The participant must **COMPREHEND** the information. The research team must evaluate the potential participant's ability to understand the proposed intervention in the study.
- ◆ The participant must **AGREE** to the proposed intervention in the research study.
- ◆ The participant's agreement must be **VOLUNTARY** and free from coercion.
- ◆ Finally, participants must be informed that even after they have made a voluntary agreement to participate in the study, they may **WITHDRAW** such agreement at any time without penalty.

Principal Investigators should be aware that informed consent, whether oral or written, **CANNOT** and **MUST NOT** include any language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence. [45 CFR §46.116]

Documentation of Informed Consent

To approve research, the IRB must determine that informed consent is appropriately documented, unless such documentation can be waived under federal regulations. There are two methods for documenting informed consent, according to 45 CFR§46.117:

1. Consent may be documented by using a written consent document that includes the eight required elements of informed consent. The consent document form must be signed by the participant or the participant's legally authorized representative and a copy must be given to whoever signs the form.
2. Alternatively, consent can be documented using a short form consent document stating that the elements of informed consent have been presented orally to the participant (or the participant's legally authorized representative). When using this method, the following is necessary:
 - (a) You must have a witness to the oral presentation.
 - (b) The IRB must approve a written summary of what is to be said to the subject or the representative.
 - (c) Only the short form itself is to be signed by the subject or the representative.
 - (d) The witness must sign both the short form and a copy of the summary.
 - (e) As the researcher actually obtaining consent, you must sign a copy of the summary.
 - (f) A copy of the summary must be given to the subject or the representative, in addition to a copy of the short form.
 - (g) The original of the signed consent form must remain with the researcher or PI.

Waivers of Informed Consent

The Common Rule regulations at 45 CFR 46.116(d) and §46.117(c) allow the IRB to approve a consent procedure that waives some or all of the elements of informed consent, or waives the requirement to obtain informed consent altogether. To approve any alteration to, or waiver of, informed consent, the IRB must find and document that:

- (1) The research involves no more than minimal risk to the subjects;
- (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (3) The research could not practicably be carried out without the waiver or alteration; and
- (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

These findings and their justifications must be clearly documented in IRB meeting minutes whenever the IRB exercises this waiver provision.

As Principal Investigator, you should use the decision flow chart given in **Figure 3** below to help you determine whether your project might be eligible for this waiver of informed consent.

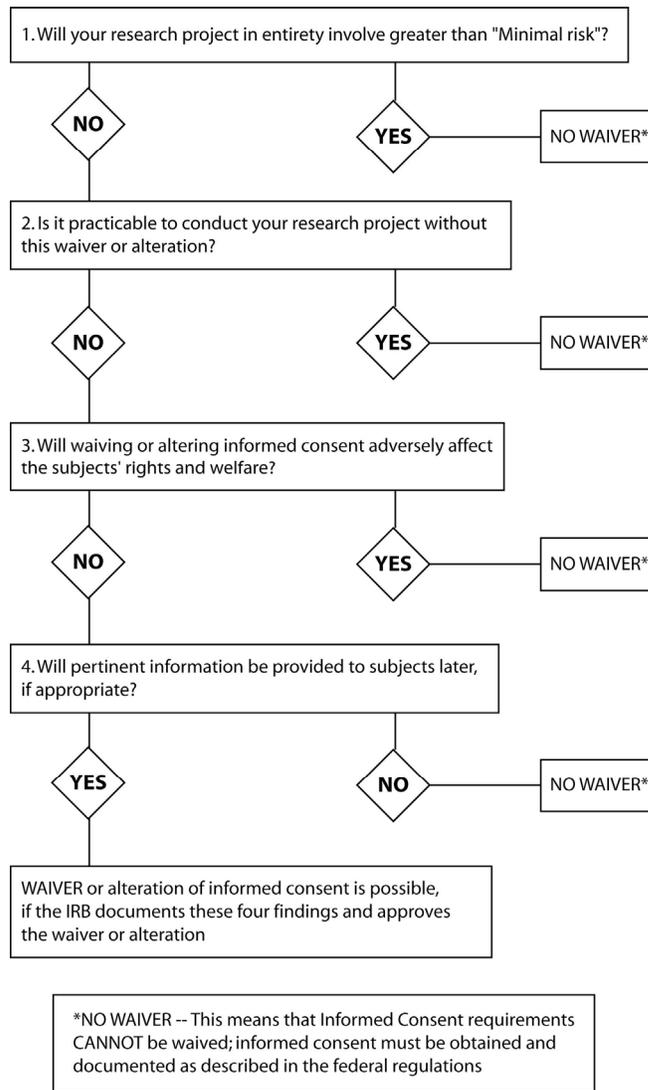


Figure 3: Decision Flow Chart showing when the IRB can waive informed consent or alter informed consent elements, according to the regulations in §46.116(d)

b. Waiver of Signed Consent Form [(§46.117(c))]

An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

- (1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- (2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

◆ **Has the risk related to this project been clearly assessed and discussed in the application?**

When specifying your project's level of risk on the Application Form, you should take the following types of risk or discomfort into consideration:

Physical Risk: Physical discomfort, pain, injury, illness or disease brought about by the methods and procedures of the research.

Psychological Risk: May be experienced during the research situation and/or later, as a result of participating. Includes anxiety, stress, fear, confusion, embarrassment, depression, guilt, shock, loss of self-esteem, and altered behavior.

Social/Economic Risk: Refers to decreases in quality of life that result from information being created or used in a way that is damaging to the individual in question. Consider whether the information being collected might cause the participant embarrassment, humiliation, discrimination, or stigmatization. Economic risks include loss of insurability, loss of wages or income, and damage to employability.

Legal Risk: Risk of criminal prosecution or civil lawsuit when research methods reveal that the subject has or will engage in conduct for which the subject or others may be criminally liable.

Loss of Confidentiality: Confidentiality is presumed and must be maintained unless the investigator obtains the express permission of the subject to do otherwise. Risks from loss of confidentiality include invasion of privacy, as well as the social, economic and legal risks outlined above.

◆ **How do you know if you have the most recent Application Form?**

Please check the IRB website at <http://www.nmt.edu/~red/IRB/> or contact the IRB Administrator to make certain that you are using the most recent version of the Application Form. The Form will be reviewed and updated as needed by the New Mexico Tech IRB to conform to any changes or amendments to the federal regulations. Completing the most recent Application Form is crucial for an accurate and thorough review in accordance with applicable guidelines and policies.

◆ **Where do you send your completed Application Form and attachments?**

Your original signed Application Form and all attachments should be sent or delivered to:

IRB Administrator
R&ED Office -- New Mexico Tech
801 Leroy Place
Socorro, NM 87801

APPROVAL PROCESS USED BY THE IRB

◆ How will your Application be reviewed and how long will the process take?

Application Forms will be reviewed by the IRB Administrator as soon as possible after their submission. The IRB Administrator will determine the required level of IRB review for the submitted protocol, using the review criteria discussed in the Policy section of this Handbook.

Administrative or Expedited Review

Research that does not require mandatory IRB review (*see Appendix A*) will be reviewed as quickly as possible by the IRB Administrator. Projects eligible for **Expedited review** (*See Appendix B*) will be reviewed and approved by the IRB Administrator and one other IRB Board member. While continuing review is not required in this category, any changes to the approved project must be submitted to the IRB Administrator before they can be implemented.

Full Board Review

Those projects slated for Full Board review will require a longer period of time for review and approval by the IRB. The IRB Administrator will make copies of the Application Form and all attachments, and distribute them to all IRB members. The protocol will be assigned a primary and secondary reviewer from the IRB. These reviewers will review the protocol in detail and contact the PI for any additional information or needed revisions. The IRB Administrator will schedule a meeting of the full IRB, and such meeting should take place at the first available opportunity when a quorum can be present. The PI will be notified in writing of the IRB's decision as soon as possible after the IRB meeting has adjourned.

NOTE: The IRB Administrator has discretion concerning level of review. If the appropriate level of review is unclear to the Administrator, or if requested by an expedited reviewer, the Application may be assigned for full board review.

◆ What does the IRB look for when deciding whether or not your project will be approved?

The IRB must base its approval or disapproval on the following factors given in 45 CFR 46.111:

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

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

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by federal regulation.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by federal regulation.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

◆ How will you know when your application has been approved?

The IRB will notify the Principal Investigator in writing of the board's approval. If the project is externally funded, the funding federal department or agency will be sent a copy of the IRB's approval letter. The approval letter will contain the relevant federal regulation citation, the approval date, the expiration date and the IRB Database tracking number.

Conditions of Approval

	IRB approval of a project applies only to the procedures submitted in the Application Form. The PI cannot make any changes to the research procedure without obtaining prior IRB approval. The PI must also report any problems that arise during the use of human subjects to the IRB immediately.
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If the IRB grants an approval with contingencies, those contingencies must be satisfied (reviewed and approved) prior to beginning the project.

IRB Approval of a research project is valid only until the expiration date. Multi-year projects must be reviewed no less than annually. (See below for the procedures for obtaining a continuation of approval.)

◆ IRB approval will expire before you finish your project. What should you do to maintain IRB approval?

With the exception of projects approved administratively, the IRB is required to reevaluate continuing research projects at intervals appropriate to the degree of risk, but not less than once a year. For research involving no more than minimal risk, the approval period is generally one year. For research involving greater than minimal risk, the IRB will determine the appropriate approval period. Your Approval Form or Letter from the IRB will list the date when IRB approval for your project will expire.

The **Continuing Review Request Form** can be accessed online at <http://www.nmt.edu/~red/IRB/> or obtained from the IRB Administrator in the R&ED Office.

The IRB Administrator will send out written reminder letters to the Primary Investigator several weeks prior to the expiration date.

Lapsed Approval procedure

	<p>If the IRB approval for your research project expires and you fail to seek a continuing review before the existing IRB approval lapses, conducting the research beyond the expiration date is a violation of federal regulations, as well as New Mexico Tech policy. You must halt all research on the project and file a completely new Application Form with the IRB in order to gain continued approval for your project.</p>
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◆ You want to change something in your project. Do you have to submit everything to the IRB again?

All changes in the project that deviate from the original submission **MUST** be approved by the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the subjects.

Researchers should complete and submit **Form C (Page 6 of the IRB Approval Form)** to the IRB for review and approval. The form can be obtained from the IRB Administrator or downloaded from the IRB website at <http://www.nmt.edu/~red/IRB/>

◆ **If someone participating in your study has an unexpected or negative reaction, what do you do?**

Any unanticipated, serious, or continuing problems encountering regarding risks to subjects must be reported immediately to the IRB Administrator via the **Adverse Event Report Form**. The form is available online at <http://www.nmt.edu/~red/IRB/> or from the IRB Administrator in the R&ED Office.

The IRB Administrator must report any adverse events as mandated in the Federal Regulations. The event must be reported in writing within 10 working days to the IRB Chair, New Mexico Tech's Vice President for Research, the funding federal department or agency, and in some cases, to the OHRP and the appropriate regulatory body.

◆ **The funding agency requires proof of IRB approval before they will release funds, but the money is needed to develop the instruments and procedures to be used in the research. What do you do?**

If your research project must receive funding before you can develop and finalize the instruments and procedures for human subject use, a special set of procedures must be followed.

This situation presents the IRB with a dilemma: The IRB is responsible for thoroughly reviewing human subject research submissions prior to awarding of funding, but a thorough review is not possible until funding is granted.

In accordance with 45 CFR 46.118 (and all correlating federal subparts distinct to each "Common Rule" agency), the following procedure will be used in this situation:

When your research project will require the use of human subjects, but the details of the project are not yet clarified, you should check the "YES" box in the Human Subjects Research section of the R&ED Proposal Routing Sheet. As PI, you should then fill out and submit an IRB Application Form to the IRB Administrator with all relevant information known at that time. You should check the "118 designation" box on the Application Form.

The IRB Administrator will enter your Application Form into the IRB's tracking database, and then send a letter to the funding agency to indicate that New Mexico Tech adheres to 45 CFR 46.118 and to verify that the research project's IRB Application Form has been received and will be reviewed when complete.

Your project's IRB Application will then be placed in **PENDING** status. **It will not be reviewed or approved with contingencies.** When you are able develop the required instruments and procedures for your research project, you should submit them in writing to the IRB Administrator. At that time, an IRB review will occur. Please be aware that you **CANNOT** use any human subjects in your research project until IRB approval has been granted. The IRB Administrator will send you written notice each quarter to remind you that IRB approval has not yet been obtained for your project and that additional items are needed to facilitate IRB review.

If you or your research staff conduct human subject research without obtaining IRB approval, the full IRB membership and Vice President for Research will be alerted immediately. A proper course of action will be pursued and could include the halting of all funds and research associated with the project and possible termination of the research project.

SPECIAL CATEGORIES OF RESEARCH

◆ Student Research

All student investigators must have a University supervisor (“Advisor”) who is responsible for ensuring that all procedures required by the IRB are complied with by the investigator. The Advisor must sign the IRB Application Form certifying that the project is under his/her supervision.

Class-related activities

The collection of information from respondents for the purpose of class discussion, or for the purpose of training in research or research methods, does NOT require IRB review, except for the types of projects listed below. Care should still be taken, however, to protect the rights and welfare of those who act as respondents.

Class-related projects that MUST be submitted to the IRB for review and approval:

- All theses and dissertations that involve human subjects.
- All projects for which findings may be published or otherwise disseminated.
- Class-related projects for which the data are collected and archived for any purpose other than administrative evaluations.

◆ Telephone Surveys

The informed consent process may be altered from the written standard in some cases where a telephone survey methodology is used. Where research is considered to be minimal risk, often consent may be obtained via telephone. The following items minimally must be included in the consent script (additional items may be required based on the subject matter and risks to subjects):

- The purpose of the research
- The researcher’s name and his/her association with New Mexico Tech
- How confidentiality of their responses will be maintained
- Participation is voluntary, the participant can refuse to answer any questions or terminate their participation at anytime.

◆ Family of Origin Research and Third Party Consent Issues

When an investigator conducting research obtains identifiable private information about a living individual, that individual becomes a research subject. For example, when asking for family medical history, if the subject is asked to identify if his/her mother or father has a condition or ailment and the original subject is identifiable, the parent then becomes a research subject. This parent would be referred to as a “third party subject” or “secondary subject” and the investigator would need to seek informed consent from them regarding the information being obtained.

An agreement to participate in research constitutes valid consent only if voluntarily given by the individual whose identifiable private information is obtained by the researcher. Thus the regulations require consideration of all living individuals about whom a researcher obtains identifiable private information, whether or not they are family members.

◆ Virtual Reality Research

Experiments involving immersive virtual environments (VEs), or virtual realities (VRs) that submerge a person's senses in virtual stimuli, should exercise all accepted human use procedures to ensure the safety of subjects. Investigators involved in this type of research should pay particular attention to the special guidelines presented in this section.

1. Experiments involving VEs for data visualization tasks or navigation/locomotion tasks in virtual reality (e.g., flying, walking, driving, etc.) should exercise all accepted human use procedures to ensure the safety of subjects and should pay particular attention to the special guidelines presented in this section.
2. Experimental VR applications should permit user interaction with virtual objects and allow the user direct control over virtual representations as well as visual motion (i.e., if possible, the user should be the locus of control).
3. Human use applications should identify all reasonable risks associated with VR exposure including:
 - a. motion sickness-like symptoms [e.g., nausea, oculomotor disturbances (hand-eye coordination errors), disorientation] due to the illusion of self-motion through visual scene changes in the absence of corresponding physical motion;
 - b. visual fatigue due to excessive stimulation of visual receptors;
 - c. muscle fatigue and localized discomfort (e.g., neck muscle fatigue due to use of a head-mounted display or the need to hold a hand control device);
 - d. drowsiness due to visual fatigue;
 - e. pacemaker malfunction due to electromagnetic fields generated by VR system devices;
 - f. startle effects due to large dynamically varying visual displays;
 - g. epileptic seizure due to electromagnetic fields and startle effects; and
 - h. becoming lost in VE due to loss of spatial orientation.

- i. Subjects must be required to provide a past history of epilepsy.
 - ii. Persons with pacemakers should be excluded from VR research.
 - iii. Persons with epilepsy should be excluded from VR research experiments as described in Items (1) and (2) and studies involving VR applications not permitting user control of virtual objects or visual motion.
4. VR experiment subjects should be advised that regardless of individual characteristics, simulator sickness symptoms have been shown to be pervasive in VR exposure and that the potential exists for all symptoms. However, the intensity may vary between different subjects.
5. All studies must employ the Simulator Sickness Questionnaire (SSQ) [Kennedy et al. (1993). *Int. J. of Avi. Psych.*, 3(3)] to ensure subject health before and after VR exposure.
 - a. Subjects should not be permitted to participate in VR research if pre-test SSQ scores indicate poor health (see Kennedy (1993) for definition of poor health).
 - b. All subjects must be required to remain at the site of the research for at least 20 minutes if post-test SSQ scores are not equal to pre-test scores. (Researchers must compare post-test SSQ scores with pre-test scores at 20-minute intervals until the scores are equal.)
 - c. If post-test SSQ scores are not equal to pre-test scores 1-hour after VR exposure, subjects must be advised not to drive for 24 hours and must be provided with transportation. Researchers should recommend that the subject consult a medical physician for motion sickness (either personal or on-site).
6. Those types of VR experiments identified in Items (1) and (2) and studies involving VR applications that do not allow the user to control virtual objects or visual motion must employ postural stability tests as an additional precautionary measure for ensuring subject health after VR exposure.

Subjects must be able to perform a one- legged standing test (using the non-preferred leg) and heel-to-toe test (with the non-preferred leg in rear) for 30 seconds. (Researchers must verify subject ability to complete these tests at 20-minute intervals until they are successful.)

Investigators who perform these types of experiments should consult with an expert in VR research and have that expert review all procedures to reduce risk to human subjects..
7. All VR research must execute a specialized informed consent procedure informing subjects of the potential for "motion sickness-like" symptoms, advising subjects to inform researchers of the onset of simulator sickness symptoms (as described above), and advising subjects that they may end VR exposure at any time.

◆ Internet Research & Use of Email

Certain types of Internet research do qualify as human subjects research. The challenge for the IRB lies in applying traditional human subject regulations to this new medium. The

investigator should be aware of the following issues when undertaking research on the Internet:

1. If documentation of consent can be waived under 45 CFR 46.117c, portals can be used to require consent (i.e., an introductory web page advising participants of the nature of the study and their rights with a button to click before allowing further access). If a signed consent form is required, the form must be signed and returned before access to the website is allowed.
2. Participation by minors is discouraged. There are several programs (e.g. Adult Check systems and Internet Monitoring software) that may be used to screen out minors.
3. Confidentiality concerns are varied: Could there be inadvertent disclosure if someone mistakenly hits the "reply to all" button when utilizing email? Is study data or other sensitive information going to be stored on a web server? Is this information vulnerable where hackers may deliberately access it? These concerns must be measured relative to the sensitivity of the information. The Internet may not be an appropriate medium for research about sensitive topics for those reasons.
4. When using electronic correspondence (email), your participants should always be advised of the confidentiality limits. Security experts describe email communication as being similar to a "postcard"; that is, virtually anyone who comes in contact with the correspondence may read it.

ADDITIONAL SAFEGUARDS FOR SPECIAL POPULATIONS

Whenever proposed research subjects may be vulnerable to injury, coercion, or undue influence, the investigator must include additional safeguards in the consent process and the study protocol to protect the potential subject's rights and welfare.

◆ Students

Universities, and the association of investigators with them, provide investigators with a ready pool of student research subjects. The problem with student participation in research conducted at the university is that their agreement to participate may not be freely given. Students may volunteer to participate out of a belief that doing so will place them in good favor with faculty (e.g., that participating will result in receiving better grades, recommendations, employment, or the like), or that failure to participate will negatively affect their relationship with the investigator or faculty in general (i.e., by seeming "uncooperative," not part of the scientific community). Prohibiting all student participation in research, however, would clearly be an overprotective reaction. An alternative way to protect against coercion is to advertise for subjects generally (e.g., through notices posted in the school or department) rather than recruit individual students directly. As with any research involving a potentially vulnerable subject population, the New Mexico Tech IRB will pay special attention to the potential for coercion or undue influence and consider ways in which the possibility of exploitation can be reduced or eliminated.

Requiring participation in research for course credit (or extra credit) is also controversial, though common in the social and behavioral sciences. Students in beginning psychology courses, for instance, might be required to serve as subjects for a given number of hours of research or in a given number of research projects. Or they might be given the option of participating for additional grade credit. In either case, students should be afforded a non-research alternative to complete course requirements or earn extra credit. This alternative should be no less attractive (e.g., in time or effort) than the research opportunity. Another concern raised by the involvement of students as subjects is confidentiality. As with research involving human subjects generally, the New Mexico Tech IRB must be made aware that research involving the collection of data on sensitive subjects such as mental health, sexual activity, or the use of illicit drugs or alcohol presents risks to subjects of which they should be made aware and from which they should be protected, to the greatest extent possible.

◆ Employees

The issues with respect to employees as research subjects are essentially identical to those involving students as research subjects: coercion or undue influence, and confidentiality. As student participation raises questions of the ability to exercise free choice because of the possibility that grades or other important factors will be affected by decisions to participate, employee research programs raise the possibility that the decision will affect performance evaluation or job advancement. It may also be difficult to maintain the confidentiality of personal medical information or research data when the subjects are also employees.

◆ Cognitively Impaired

The predominant ethical concern in research involving individuals with psychiatric, cognitive, or developmental disorders, or who are substance abusers is that their disorders may compromise their capacity to understand the information presented and their ability to make a reasoned decision about participation. Many individuals with disabilities affecting their reasoning powers may be residents of institutions responsible for their total care and treatment. The impact of institutionalization may further compromise their ability to exercise free choice (voluntariness). (These concerns apply both to voluntary patients and those committed involuntarily.) It is important to protect the privacy of all subjects and the confidentiality of information gathered in research exploring emotionally sensitive topics.

It is now generally accepted that research involving persons whose autonomy is compromised by disability or restraints on their personal freedom should bear some direct relationship to their condition or circumstances. Persons who are institutionalized, particularly if disabled, should not be chosen for studies that bear no relations to their situation just because it would be convenient for the researcher.

Consent to research involving cognitively impaired subjects through any of the intramural programs of the NIH is guided by NIH policy on consent to research with impaired human subjects. This policy sets out, in matrix form, conditions under which cognitively impaired subjects may participate in research of varying risk.

As a general rule, the New Mexico Tech IRB requires that all adults, regardless of their diagnosis or condition, should be presumed competent to consent unless there is evidence of serious mental disability that would impair reasoning or judgment. Even those who do have a diagnosed mental disorder may be perfectly able to understand the matter of being a research volunteer, and quite capable of consenting to or refusing participation. Mental disability alone should not disqualify a person from consenting to participate in research; rather, there should be specific evidence of individuals' incapacity to understand and to make a choice before they are deemed unable to consent.

Persons formally adjudged incompetent have a court-appointed guardian who must be consulted and who can give consent on their behalf. Officials of the institution in which incompetent patients reside are not generally considered appropriate, since their supervisory duties may give rise to conflicting interest and loyalties. Family members or others financially responsible for the patient may also be subject to conflicting interests because of financial pressures, emotional distancing, or other ambivalent feelings common in such circumstances.

◆ Children

The special vulnerability of children makes consideration of involving them as research subjects particularly important. To safeguard their interests and to protect them from harm, special ethical and regulatory considerations apply for reviewing research involving children. For the purposes of this Policy, "children" includes all human subjects who have not yet reached their 18th birthday (e.g., 0 through 17 years old).

Four Approved Categories of Research Involving Children

The IRB may approve research involving children only if special provisions are met and the research falls into one of four categories. The four categories of research involving children that may be approved by IRBs are based on degree of risk and benefit to individual subjects.

1. Research not involving more than Minimal Risk

When the IRB finds that no greater than minimal risk to children is presented, the IRB may approve the proposal only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

2. Research involving greater than Minimal Risk but presenting the prospect of direct benefit to the individual subjects.

If the IRB finds that more than minimal risk to children is presented by an intervention or procedure, but that the intervention or procedure holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, the IRB may approve the research only if the IRB finds that:

1. the risk is justified by the anticipated benefit to the subjects;
2. the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
3. adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth below.

3. Research involving greater than Minimal Risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

If the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, the IRB may approve the research only if the IRB finds that:

1. the risk represents a minor increase over minimal risk;
2. intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
3. the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
4. adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth below.

4. Research not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If the IRB does not believe the research proposal meets any of the requirements set forth above, it may still approve the application but only if:

1. the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
2. the Secretary of the Department of Health and Human Services, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
 - (a) that the research in fact satisfies one of the conditions set forth above, or
 - (b) the following: (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) the research will be conducted in accordance with sound ethical principles; and (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth below.

Requirements for Permission by Parents or Guardians and for Assent by Children

Adequate Provisions for Child's Assent

The investigator must make adequate provisions for soliciting the assent of child subjects when the children are capable of providing assent. In determining whether children are capable of assenting, the investigator should take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child. The child should be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity, and condition. See Appendix E for sample assent language.

Assent Defined. "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Waiver of Assent

If the IRB determines either of the following to be true, then the assent of the children is not a necessary condition for proceeding with the research:

- The capability of some or all of the children is so limited that they cannot reasonably be consulted; or
- When the research offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research.

Child's Dissent. Additionally, in such circumstances a child's dissent, which should normally be respected, may be overruled by the child's parents, at the IRB's discretion. When research involves the provision of experimental therapies for life-threatening diseases such as cancer, however, the IRB should be sensitive to the fact that parents may wish to try anything, even when the likelihood of success is marginal and the probability of extreme discomfort is high. Should the child not wish to undertake such experimental therapy, difficult decisions may have to be made. In general, if the child is a mature adolescent and death is imminent, the child's wishes should be respected.

Finally, even where the IRB determines that the child subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived for adults.

Adequate Provisions for Parents' or Guardian's Permission

The investigator must make adequate provisions for soliciting the permission of each child's parents or legally authorized representative.

Research not involving greater than minimal risk.

Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research not involving greater than minimal risk. Minimal risk means that 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. An example of minimal risk is the risk of drawing a small amount of blood from a healthy individual for research purposes (because the risk of doing so is no greater than the risk of doing so as part of a routine physical examination).

Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

Where parental permission is to be obtained, the permission of one parent may be sufficient for research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects when the IRB finds that the intervention or procedure holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, and the IRB finds that:

1. the risk is justified by the anticipated benefit to the subjects;
2. the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
3. adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

When the research involves greater than minimal risk to children and involves an intervention

or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. Additionally, the IRB must find that:

1. the risk represents a minor increase over minimal risk;
2. the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
3. the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
4. adequate provisions are made for soliciting assent of the children and permission of their parents or guardians

Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

When the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and the Secretary of the Department of Health and Human Services approves the research, and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

Waiver of Parental or Guardian Permission

If parental or legally authorized representative permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), the investigator may request that the IRB waive the consent requirements described above, provided both (i) an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and (ii) the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

Documentation of parental/guardian permission

Permission by parents or guardians shall be documented in the same manner as required for other subjects. When the IRB determines that assent of a child is required, it shall also determine whether and how assent must be documented.

◆ Wards of the State or Other Agency

Children who are wards of the state or any other agency, institution, or entity can be included

in research that falls into one of two categories. Additionally, the research must be: (i) related to their status as wards; or (ii) conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

Category 1: Research involving greater than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge about the Subject's Disorder or Condition

If the IRB finds that more than minimal risk to wards is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, the IRB may approve the research only if the IRB finds that:

1. the risk represents a minor increase over minimal risk;
2. the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
3. the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
4. adequate provisions are made for soliciting assent of the children and permission of their guardians.

Category 2: Research Which Presents an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting the Health or Welfare of Wards

The IRB may also approve a protocol which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of wards, and

1. the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of wards; and
2. the Secretary of the Department of Health and Human Services, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:
 - i. that the research in fact satisfies one of the conditions set forth above, or
 - ii. the following: (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of wards; (ii) the research will be conducted in accordance with sound ethical principles; and (iii) adequate provisions are made for soliciting the assent of children and the permission of their guardians.

If the research is approved under this authority, the IRB must require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of

the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

◆ **Pregnant Women and Fetuses**

This guidance applies to all research, development, and related activities involving: (i) the fetus, (ii) pregnant women, and (iii) human in vitro fertilization and is based on the Federal Regulations at 45 CFR 46 Subpart B. The requirements regarding these subjects are in addition to those imposed under the other IRB policies and other applicable federal, state and local laws.

Research involving women who are or may become pregnant should receive special attention from investigators because of women's additional health concerns during pregnancy and because of the need to avoid unnecessary risk to the fetus. Further, in the case of a pregnant woman, the investigator must consider when the informed consent of the father to the research is required. Special attention is justified because of the involvement of a third party (the fetus) who may be affected but cannot give consent and because of the need to prevent harm or injury to future members of society. Procedural protections beyond the basic requirements for protecting human subjects are prescribed in federal regulations for research involving pregnant women.

Definitions used in this section

- a. "Pregnancy" encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.
- b. "Fetus" means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable.
- c. "Viable" as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. If a fetus is viable after delivery, it is a premature infant.
- d. "Nonviable fetus" means a fetus ex utero which, although living, is not viable.
- e. "Dead fetus" means a fetus ex utero which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).
- f. "In vitro fertilization" means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

Additional Requirements For Activities Involving Fetuses, Pregnant Women, or Human in Vitro Fertilization

In addition to all other requirements for approval, the IRB must determine that:

- a. adequate consideration has been given to the manner in which potential subjects will be selected; and
- b. adequate provision has been made by the investigator for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the IRB or subject advocates in (i) overseeing the actual process by which individual consents are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen).

Activities Directed Toward Pregnant Women as Subjects

No pregnant woman may be involved as a subject unless: (1) the purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

Father's Consent

An activity permitted under the above mentioned criteria may be conducted only if the mother and father are legally competent and have both given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (i) the purpose of the activity is to meet the health needs of the mother; (ii) his identity or whereabouts cannot reasonably be ascertained; (iii) he is not reasonably available; or (iv) the pregnancy resulted from rape.

Activities Directed Toward Fetuses in Utero as Subjects

No fetus in utero may be involved as a subject in any research activity unless the IRB determines either: (i) the purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (ii) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

Father's Consent

If such an activity is approved, it may be conducted only if the mother and father are legally competent and have both given their informed consent, except that the father's consent need not be secured if: (i) his identity or whereabouts cannot reasonably be ascertained, (ii) he is not reasonably available, or (iii) the pregnancy resulted from rape.

Activities Directed Toward Fetuses ex Utero, Including Nonviable Fetuses, as Subjects

Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject unless: (i.) there will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or (ii.) the purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

Nonviable Fetuses

No nonviable fetus may be involved as a subject unless: (i.) vital functions of the fetus will not be artificially maintained, (ii.) experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and (iii.) the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

Parental Consent

Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects may be conducted only if the mother and father are legally competent and have both given their informed consent, except that the father's informed consent need not be secured if: (i) his identity or whereabouts cannot reasonably be ascertained, (ii) he is not reasonably available, or (iii) the pregnancy resulted from rape.

Activities Involving the Dead Fetus, Fetal Material, or the Placenta

Activities involving the dead fetus, macerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities. For example, Tennessee Code Annotated section 39-15-208 makes it unlawful for any person or entity to engage in medical experiments, research, or the taking of photographs upon an aborted fetus without the prior knowledge and consent of the mother. Additionally, no person or entity may offer or accept money or anything of value for an aborted fetus. Violations of these provisions are punishable as a Class E felony.

Modification or Waiver of Specific Requirements

Upon the request of the investigator (with the approval of the IRB), the Secretary of the Department of Health and Human Services may modify or waive any of the above requirements of this Policy.

Studies in Which Pregnancy is Coincidental to Subject Selection

Any study in which women of childbearing potential are possible subjects may inadvertently include pregnant women. Federal regulations require that, when appropriate, subjects be provided a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable as part of the informed consent process.

In some studies, the investigator may need to ensure that nonpregnant subjects are advised to

avoid pregnancy or nursing for a time during or following the research. Furthermore, where appropriate, subjects should be advised to notify the investigator immediately should they become pregnant. In some instances there may be potential risk sufficient to justify requiring that pregnant women either be specifically excluded from the research or studied separately.

GLOSSARY

Code of Federal Regulations (CFR)	The listing of federal laws that have been passed by the United States Congress and signed into law by the President of the United States.
The Common Rule	The federal regulations listed in 45 CFR Part 46 and which were enacted on June 18, 1991 to protect the rights and welfare of human subjects in research.
Department of Health and Human Services (DHHS)	The federal agency that oversees the federal Office for Human Research Protections, and which is ultimately responsible for enforcing the Common Rule.
Federal Wide Assurance (FWA)	A legally-binding agreement that formalizes a research institution's commitment to protect human subjects. Federal policy requires that each institution engaged in federally-supported human subjects research must obtain an FWA from the DHHS.
Human Subject	A living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. [45 CFR §46.102]
Identifiable Private Information	Addresses, numbers, and/or demographic information that may be used to link the information back to a specific individual. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.
Institutional Review Board (IRB)	A specially appointed ethics committee that reviews all research projects involving human subjects to ensure that the rights and welfare of such subjects are being protected in accordance with the Common Rule.
Interaction	Communication or interpersonal contact between investigator and subject.
Intervention	Includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
Minimal Risk	A research project involves "Minimal Risk" if the participant experiences no pain or physical danger; experiences no emotional arousal or psychological stress beyond the level normally expected in everyday life; the project neither includes nor attempts to induce long-term significant change in the participant's behaviors; the data gathered would not embarrass or socially disadvantage the participant if confidentiality were violated; and if there is no reason

	to believe that the subject would choose not to participate if he or she were not aware of the specific purpose of the project. [45 CFR §46.102(i)]
Office for Human Research Protections (OHRP)	The federal office that is directly responsible for enforcing the federal regulations given in 45 CFR Part 46.
Principal Investigator (PI)	The lead researcher who is responsible for performing a research project and/or overseeing all aspects of a given research project.
Research	A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this handbook, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. [45 CFR §46.102(d)]
Research Protocol	A complete written description of the proposed research project, including an explanation of how the human subjects will be utilized in the project.

APPENDIX A – TYPES OF RESEARCH THAT ARE EXEMPT FROM MANDATORY IRB REVIEW

From: 45 CFR §46.101(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 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.

APPENDIX B – TYPES OF RESEARCH THAT QUALIFY FOR EXPEDITED REVIEW

From: 45 CFR §46.110

Applicability

(A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

(B) The categories in this list apply regardless of the age of subjects, except as noted.

(C) The expedited review procedure may NOT be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

(D) The expedited review procedure may not be used for classified research involving human subjects.

(E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

(F) Categories One (1) through Seven (7) below pertain to both initial and continuing IRB review.

Research Categories

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture, as follows:

(a) from healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples include:

(a) hair and nail clippings in a nondisfiguring manner;

(b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

(c) permanent teeth if routine patient care indicates a need for extraction;

(d) excreta and external secretions (including sweat);

(e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;

(f) placenta removed at delivery;

(g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;

(h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

(i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

(j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples include:

(a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

(b) weighing or testing sensory acuity;

(c) magnetic resonance imaging;

(d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

(e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

(b) where no subjects have been enrolled and no additional risks have been identified;
or

(c) where the remaining research activities are limited to data analysis.

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

APPENDIX C – ARE YOU ENGAGED IN HUMAN SUBJECTS RESEARCH?

Reprinted From: <http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm>

Institutions or Researchers WOULD be considered "engaged" in human subjects research if their involvement includes the following:

- A. Institutions whose employees or agents intervene with living individuals by performing invasive or noninvasive procedures for research purposes (e.g., drawing blood; collecting other biological samples; dispensing drugs; administering other treatments; employing medical technologies; utilizing physical sensors; utilizing other measurement procedures).
(**Agents** include all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility.)
- B. Institutions whose employees or agents intervene with living individuals by manipulating the environment for research purposes (e.g., controlling environmental light, sound, or temperature; presenting sensory stimuli; orchestrating environmental events or social interactions; making voice, digital, or image recordings).
- C. Institutions whose employees or agents interact with living individuals for research purposes (e.g., engaging in protocol-dictated communication or interpersonal contact; conducting research interviews; obtaining informed consent). (See next section for certain informational activities that do not constitute "engagement" in research.)
- D. Institutions whose employees or agents release individually identifiable private information, or permit investigators to obtain individually identifiable private information, without subjects' explicit written permission (e.g., releasing patient names to investigators for solicitation as research subjects; permitting investigators to record private information from medical records in individually identifiable form). (However, see Example (B)(5) regarding release of such information with subjects' prior, written permission, and Example (B)(6) regarding release of such information to State Health Departments.)
- E. Institutions whose employees or agents obtain, receive, or possess private information that is individually identifiable (either directly or indirectly through coding systems) for research purposes (e.g., obtaining private information from medical records in an individually identifiable form). (However, see Examples (B)(7) and B(8) for certain activities involving the release of information and/or specimens to investigators in non-identifiable form.)
- F. Institutions whose employees or agents obtain, receive, or possess private information that is individually identifiable (either directly or indirectly through coding systems) for the purpose of maintaining "statistical centers" for multi-site collaborative research. Where institutional activities involve no interaction or intervention with subjects, and the principal risk associated with institutional activities is limited to the potential harm resulting from breach of confidentiality, the Institutional Review Board (IRB) need not review each collaborative protocol. However, the IRB should determine and document that the statistical

center has sufficient mechanisms in place to ensure that (i) the privacy of subjects and the confidentiality of data are adequately maintained, given the sensitivity of the data involved; (ii) each collaborating institution holds an applicable OHRP-approved Assurance; (iii) each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects; and (iv) informed consent is obtained from each subject in compliance with HHS regulations.

- G. Institutions whose employees or agents maintain "operations centers" or "coordinating centers" for multi-site collaborative research. Where institutional activities involve no interaction or intervention with subjects, the IRB need not review each collaborative protocol. However, the IRB should determine and document that the operations or coordinating center has sufficient mechanisms in place to ensure that (i) management, data analysis, and Data Safety and Monitoring (DSM) systems are adequate, given the nature of the research involved; (ii) sample protocols and informed consent documents are developed and distributed to each collaborating institution; (iii) each collaborating institution holds an applicable OHRP-approved Assurance; (iv) each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects; (v) any substantive modification by the collaborating institution of sample consent information related to risks or alternative procedures is appropriately justified; and (vi) informed consent is obtained from each subject in compliance with HHS regulations.
- H. Institutions receiving a direct HHS award to conduct human subjects research, even where all activities involving human subjects are carried out by a subcontractor or collaborator (e.g., a small business receives a HHS award to design a medical device at its own facility and contract with a medical clinic to test the device with human subjects; a foundation receives a HHS award on behalf of an affiliated institution that will actually conduct the human subjects research).

Institutions would NOT be considered "engaged" in human subjects research if their involvement is limited to the following:

- A. Institutions whose employees or agents act as consultants on research but at no time obtain, receive, or possess identifiable private information (e.g., a consultant analyzes data that cannot be linked to individual subjects, either directly or indirectly through coding systems, by any member of the research team).
1. Should a consultant access or utilize individually identifiable private information while visiting the research team's institution, the consultant's activities become subject to the oversight of the research team's Institutional Review Board (IRB). However, the consultant's institution is not considered to be "engaged" in the research.
 2. Should a consultant obtain "coded" data for analysis at the consultant's institution, the consultant's institution is considered "engaged" in human subjects research, and would need an Assurance, unless a written agreement unequivocally prohibits release of identifying codes to the consultant.

- B. Institutions whose employees or agents (i) perform commercial services for the investigators (or perform other genuinely non-collaborative services meriting neither professional recognition nor publication privileges), and (ii) adhere to commonly recognized professional standards for maintaining privacy and confidentiality (e.g., an appropriately qualified laboratory performs analyses of blood samples for investigators solely on a commercial basis).
- C. Institutions whose employees or agents (i) inform prospective subjects about the availability of research; (ii) provide prospective subjects with written information about research (which may include a copy of the relevant informed consent document and other IRB-approved materials) but do not obtain subjects' consent or act as authoritative representatives of the investigators; (iii) provide prospective subjects with information about contacting investigators for information or enrollment; or (iv) obtain and appropriately document prospective subjects' permission for investigators to contact them (e.g., a clinician provides patients with literature about a research study, including a copy of the informed consent document, and tells them how to contact the investigator if they want to enroll; a clinician provides investigators with contact information about potential subjects after receiving explicit permission from each potential subject).
- D. Institutions (e.g., schools, nursing homes, businesses) that permit use of their facilities for intervention or interaction with subjects by research investigators (e.g., a school permits investigators to test students whose parents have provided written permission for their participation; a business permits investigators to solicit research volunteers at the worksite).
- E. Institutions whose employees or agents release identifiable private information to investigators with the prior written permission of the subject (e.g., with written permission of the subject, a clinician releases the subject's medical record to investigators).
- F. Institutions whose employees or agents release identifiable private information or specimens to a State or Local Health Department or its agent for legitimate public health purposes within the recognized authority of that Department. However, utilization of such information or specimens by Department investigators for research purposes would constitute engagement in research, and would require an Assurance from the Department.
- G. Institutions whose employees or agents release information and/or specimens to investigators in non-identifiable (i.e., non-linkable) form, where such information/specimens have been obtained by the institution for purposes other than the investigators' research (e.g., nursing home employees provide investigators with a data set containing medical record information, but the data set contains no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by the investigators or by nursing home personnel; a hospital pathology department releases excess tissue specimens and relevant medical record information to investigators, but these materials include no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by investigators or by hospital personnel, including the pathology department; consistent with applicable law or recognized authority, local hospitals or health departments permit State or Local Health Department investigators to access information for research purposes, but the investigators record no direct or indirect identifiers through which the identity of individual subjects could be ascertained, either by

the investigators or by local hospital or health department personnel.)

H. Institutions whose employees or agents receive information or specimens for research from established repositories operating in accordance with (i) an applicable OHRP-approved Assurance; (ii) OHRP guidance (see <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm>); and (iii) written agreements unequivocally prohibiting of release of identifying information to recipient investigators.

I. Institutions (or private practitioners) whose clinical staff provide protocol-related care and/or follow-up to subjects enrolled at distant sites by clinical trial investigators in OHRP-recognized Cooperative Protocol Research Programs (CPRPs). In such cases, (i) the CPRP clinical trial investigator (consistent with a registered investigator as defined in Section 14.1 of the NCI Investigator's Handbook) retains responsibility for oversight of protocol related activities; (ii) clinical staff may not accrue subjects or obtain informed consent for research participation; (iii) clinical staff may only provide data to the investigator in accord with the terms of informed consent; and (iv) the informed consent document should state that such data are to be provided by clinical staff as directed by the investigator.

APPENDIX D – THE NUREMBERG CODE

From "Trials of War Criminals before the Nuremberg Military Tribunals Under Control Council Control law No. 10," vol. 2, Nuremberg, October 1946 – April 1949. (Washington, DC. U.S. Government Printing Office, 1949), pp 181 – 182.

The great weight of the evidence before us is to the effect that certain types of medical experimentation on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts.

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seemed to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably [sic] cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

APPENDIX E – THE BELMONT REPORT

Ethical Principles & Guidelines for Research Involving Human Subjects

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 the rapy 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 of 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 consequence. 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 flagrant 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 disable 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.

Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful assembling 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 harm 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 IRBs 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.