Introduction

This tutorial provides an introduction to the Health and Human Services (HHS) Regulations for the Protection of Human Subjects at Title 45 Code of Federal Regulations Part 46. The HHS Regulations are intended to implement the basic ethical principles governing the conduction of human subjects research. These ethical principles are set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the “Belmont Report”).

The Belmont Report
The Belmont Report sets forth three basic ethical principles for the conduct of human subjects research:

- **Respect for persons**
  - Respect individual autonomy
  - Protect individuals with reduced autonomy

- **Beneficence**
  - Maximize benefits and minimize harms

- **Justice**
  - Equitable distribution of research burdens and benefits

Application of the general ethical principles to the conduct of human subjects research leads to the following requirements:

- **Respect for persons**
  - Informed consent
  - Protecting privacy and maintaining confidentiality
  - Additional safeguards for protection of subjects likely to be vulnerable to coercion or undue influence
• **Beneficence**
  - IRB assessment of risk/benefit analysis, including study design
  - Ensure that risks to subjects are minimized
  - Risk justified by benefits of the research

• **Justice**
  - Ensure that selection of subjects is equitable

### HHS Regulations

HHS regulations include additional protections for vulnerable populations as subparts of 45 CFR Part 46:

**Subpart B** - Additional HHS Protections for Pregnant Women, Human Fetuses and Neonates involved in Research

**Subpart C** - Additional HHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

**Subpart D** - Additional HHS Protections for Children Involved as Subjects in Research

### Definitions

**Research** - A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of the HHS regulations, 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 that qualify as “research” under the HHS regulations.

The following activities are deemed **not to be** research: Scholarly and journalistic activities (e.g.: oral history, journalism, biography, literary criticism, legal research and historical scholarship) including the collection and use of information that focuses directly on the specific individuals about whom the information is collected.

**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.

### Exempt Research

Certain research is exempt from the requirements of the HHS regulations. A determination that research is exempt does not imply that investigators have no ethical responsibilities to subjects in such research; it means only that the regulatory requirements related to IRB review, informed consent, and assurance of compliance do not apply to the research. OHRP recommends that institutions adopt clear procedures under which the IRB, or some authority other than the investigator, determines whether proposed research is exempt from the HHS regulations for the protection of human subjects. OHRP’s Exempt Research Determination FAQs say the following: "OHRP recommends that, because of the potential for conflict of interest, investigators should not be given the authority to make an independent determination that human subjects research is exempt."
Basic Provisions of the HHS Regulations

The HHS regulations contain three basic provisions for the protection of human subjects:

- Institutional assurances of compliance
- IRB review
- Informed consent

Institutional Assurances of Compliance

What is an Institutional Assurance of Compliance? Documentation of an institutional commitment to comply with HHS regulations for the protection of human subjects.

HHS will conduct or support non-exempt research covered by the regulations only if:

- the institution has an OHRP-approved Assurance,
- the institution has certified to the HHS that the research has been reviewed and approved by an IRB.

Institutional Review Board (IRB)

The Institutional Review Board (IRB) is a committee established to protect the rights and welfare of human research subjects involved in research activities.

IRB Membership

IRBs must have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB must be sufficiently qualified through the experience and expertise of its members and the diversity of its members--including considerations of race, gender, and cultural backgrounds and sensitivity to issues such as community attitudes--to promote respect for its advice and counsel in safeguarding the right and welfare of human subjects.

In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of subjects.

Every nondiscriminatory effort must be made to ensure that the IRB does not consist entirely of men or entirely of women. No IRB may consist entirely of members of one profession. Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in non-scientific areas. Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
No IRB may have a member participate in the review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

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

Except when an expedited review procedure is used, the IRB must review research at convened IRB meetings at which a majority of the IRB members are present, including one member whose primary concerns are in nonscientific areas.

**Expedited Review**

HHS regulations allow some categories of minimal risk research to be reviewed by the IRB through an expedited review procedure. Expedited review may be carried out by the IRB chairperson or by one or more experienced IRB members designated by the chairperson. All of the requirements for IRB approval of research apply to expedited review. Expedited review should not be viewed as a less rigorous review. Under expedited review, the reviewers may exercise all of the authorities of the IRB, except that the reviewers may not disapprove the research.

**IRB Review of Research**

An IRB must review all research activities covered by the HHS regulations, including proposed changes in previously approved human subjects research, and have the authority to approve, require modifications to secure approval, or disapprove any research activity. An IRB has the authority to suspend or terminate approved research that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval must include a statement of the reason for the IRB action and must be reported promptly to the investigator, appropriate institutional officials, and HHS. Research approved by the IRB may be subject to further review and approval or disapproval by institutional officials. However, institutional officials may not approve the conduct of human subjects research covered by HHS regulations that has not been approved by the IRB.

**Informed Consent**

Unless specifically authorized by the IRB, no investigator may involve a human being as a subject in research covered by HHS regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. Informed consent is the voluntary choice of an individual to participate in research based on an accurate understanding of its purposes, procedures, risks, benefits, alternatives, and any other factors that may affect a person's decision to participate. Unless specifically waived by the IRB, informed consent must be documented by a written consent form approved by the IRB and signed by the subject or by the subject's legally authorized representative. Detailed information on the Informed Consent process may be found in Module 2.
Module 2: Investigator Responsibilities and Informed Consent

Investigator Responsibilities

Investigators have the primary responsibility for protecting the rights and welfare of human research subjects and are responsible for complying with all applicable provisions of their institution's Assurance.

Investigators are responsible for:

- Conducting their research according to the IRB-approved protocol and complying with all IRB determinations;
- Obtaining and documenting the informed consent of each subject or each subject's legally authorized representative, unless the IRB has waived these requirements;
- Ensuring that each potential subject understands the nature of the research and participation;
- Providing a copy of the IRB-approved informed consent document to each subject or the subject's legally authorized representative at the time of consent, unless the IRB has specifically waived this requirement (all signed consent documents are to be retained for at least 3 years after the completion of the research and according to institutional policy).

The Consent Process

Informed consent is not a single event or just a form to be signed. Rather, it is an ongoing process that takes place between the investigator and the subject.

The basic concepts of the consent process include:

- full disclosure of the nature of the research and the subject's participation, adequate comprehension on the part of the potential subject, and
- the subject’s voluntary choice to participate.

General Requirements

Informed consent must be prospectively obtained from the subject or a legally authorized representative of the subject (if allowed by state law).

Information must be conveyed in language that is understandable to the subject or the subject’s legally authorized representative.

The subject must be given sufficient opportunity to consider whether or not to participate. Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research.
Consent must be sought only under circumstances that minimize the possibility of coercion or undue influence.

Informed consent may not include any exculpatory language. For example, subjects must not be made to give up legal rights or be given the impression that they are being asked to do so.

**Comprehension**

Even though the IRB has approved a consent procedure, it is the investigator’s responsibility to ensure that each potential subject understands the information and to take the appropriate steps necessary to gain that comprehension.

Individuals may not be involved as research subjects unless (a) they understand the information that has been provided and informed consent has been obtained, or (b) the IRB has approved a waiver for informed consent of the subject.

**Elements of Informed Consent**

HHS regulations detail specific elements of information that must be provided to each research subject unless the IRB has approved a waiver or alteration of these requirements. Basic elements of informed consent include a:

- a statement that the study involves research, an explanation of the purposes of the research, the expected length of the subject’s participation a description of the procedures to be followed, and identification of procedures which are experimental in nature;
- a description of any reasonably foreseeable risks or discomforts to the subject;
- a description of any benefits, to the subject or others which may reasonably be expected from the research;
- a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
- an explanation of whom to contact for pertinent questions about the research and research subjects rights;
- an explanation of whom to contact in the event the subject experiences a research-related injury; and
- a statement that participation is voluntary and refusal to participate will not result in penalty or loss of benefits to which the subject is otherwise entitled and the subject may withdraw at any time without penalty or loss of benefits to which the subject is entitled.

**Risks**

All reasonably foreseeable risks, discomforts, inconveniences, and harms that are associated with the research activity should be described. Investigators should be forthcoming about risks and not understate or gloss over reasonably foreseeable risks. If additional risks are identified during the course of the research, the consent process and documentation will require revisions, and subjects previously consented may need to be re-contacted and informed of the additional risks.

**Benefits**

Any benefits to subjects or others that may reasonably be expected from the research should be described. Investigators should be frank about benefits and not overestimate or magnify the possibility of benefit to the subject. If there is no reasonable expectation of benefit, the subject should
be told this. Payment to subjects should not be listed or described as a benefit of participating in the research.
Confidentiality Protections

HHS regulations require that subjects be told the extent, if any, to which confidentiality of research records identifying the subject will be maintained. For example, sponsors, funding agencies, regulatory agencies, and the IRB may review research records. Some studies may need sophisticated encryption techniques to prevent confidentiality breaches or may need a Certificate of Confidentiality to protect the investigator from being compelled to release (e.g., under subpoena) subjects' names or identifiable private information.

Contact Persons

The regulations require that the subject be provided with information on who to contact to answer questions about the research and the rights of research subjects. Subjects must also be informed of whom to contact in the event of any research-related injuries. This information must be explicitly stated and addressed in the consent process and documentation.

A single contact person is not likely to be sufficient to answer all questions. This is in part because of real or apparent conflicts of interest. Questions about the research are frequently best answered by the investigator(s). However, questions about the rights of research subjects may best be referred to persons not on the research team. These questions could be addressed to the IRB, an ombudsperson, an ethics committee, or other informed individual or committee. Each consent document may have at least two names with local telephone numbers for contacts to answer questions in these specified areas.

Voluntary Participation

The regulations require statements regarding voluntary participation and the right to withdraw at any time. Subjects must be informed that participation is voluntary, participation may be discontinued at any time, and there is no penalty or loss of benefits for refusing to participate or discontinuing participation.

Additional Protections for Vulnerable Populations

Incompetent adults cannot give consent. This may include the developmentally disabled, the cognitively-impaired, elderly, and unconscious or inebriated individuals. Only legally authorized representatives in accordance with state law can give consent for incompetent adults to participate in research.

Additionally, when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards shall be included in the study to protect the rights and welfare of these subjects.

Documentation of Consent

Except as noted below, informed consent must be documented by use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy will be given to the person signing the form.

The purpose of the written presentation of information in the consent form is to document the basis for consent and provide the subject future reference. The consent document should be revised when deficiencies are noted or when additional information will improve the consent process. All revisions
must be reviewed and approved by the IRB before a revised consent form may be used to enroll a subject.

The information that is given to the prospective subject, or his/her legally authorized representative, must be in language understandable to the subject or representative.

Consent forms should be written at a level appropriate to the understanding of the subjects to be enrolled; technical language should be avoided.

OHRP strongly discourages use of the "first person" statement in consent documents (using, "I have been fully informed about..."). Such statements unacceptably ask subjects to make statements that the subject is not in a position to verify (e.g., the subject has no way to verify that the investigator has provided full and complete information).

The consent form is merely the documentation of informed consent and does not, in and of itself, constitute informed consent.

The fact that a subject signed a consent form does not mean that he/she understood what was being agreed to or truly gave their voluntary consent.

**Waiver of Documentation of Consent**

The IRB may waive the requirement for written documentation of consent in cases where:

- The principal risks are those associated with a breach of confidentiality concerning the subject's participation in the research; and the consent document is the only record linking the subject with the research. Each subject will be asked whether or not they want to retain the documentation linking them with the research, and the subject's wishes will govern.

- OR

- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.

- OR

- The subjects are members of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk of harm to subjects, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.
Module 3:
Human Research Protections Program (HRPP)

Administrative procedures related to an HRPP may be handled differently from one institution to another. The following describes some of the responsibilities that are included in establishing an HRPP.

Institutional Review Board Responsibilities

Review by an IRB is the cornerstone of an institution's program for the protection of human subjects. IRBs are responsible for ensuring that the rights and welfare of the subjects are adequately protected.

Although many institutions will have their own IRB, institutions have the option of relying on the IRB of another institution to review their research.

IRB Authority

To approve, require modifications in to secure approval, or disapprove all research activities covered by the HHS regulations, including proposed changes in ongoing, previously approved, human subjects research. To suspend or terminate the approval of ongoing, previously approved research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected, serious harm to subjects.

Review of Performance Sites

For performance sites for which the IRB does not regularly conduct reviews, the IRB must obtain effective input on the local research context from knowledgeable persons other than those conducting the research.

IRB Communication

IRBs must provide the investigators and the institution with written notification of decisions to approve or disapprove research and of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, the written notification must include reasons for the decision and give the investigator an opportunity to respond in person or in writing.

Criteria for IRB approval of research:

In order to approve research, IRBs must find that:

- risks to subjects are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risks;
- risks to subjects are reasonable in relation to anticipated benefits, if any, to the 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;
- 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; and
• informed consent will be sought from each subject or the subject’s legally authorized representative; informed consent will be appropriately documented, in accordance with, and to the extent required by the HHS regulations.

Additional criteria for IRB approval as appropriate:

• the research plan makes adequate provision for monitoring the data collected to ensure subject safety;
• there are adequate provisions to protect the privacy of the subjects and confidentiality of data;
• when some of all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards are included to protect the rights and welfare of these subjects.
Protecting Human Research Participants:
Quiz Questions

Please record your answers on the answer key on the next page, sign (type name and date) the form and submit to hsirb@davidson.edu. A certificate indicating completion of training will be issued upon receipt.

1. An institutionally designated authority, other than the investigator, should determine that proposed studies are exempt from regulatory requirements.
   a) True
   b) False

2. A “systematic investigation designed to develop or contribute to generalizable knowledge” may include:
   a) Evaluation
   b) Research Development
   c) Testing
   d) All of the above

3. The three fundamental principles of informed consent are:
   a) Voluntariness, Privacy, Respect
   b) Voluntariness, Comprehension, Disclosure
   c) Benefits, Comprehension, Privacy
   d) Disclosure, Comprehension, Privacy

4. The regulations strongly suggest but do not require that the informed consent process be delivered in a language that is understandable to the subject.
   a) True
   b) False

5. What is an appropriate method for maintaining confidentiality of private information obtained from human subjects?
   a) Keeping data in a password-protected database
   b) Storing images in a secured cabinet
   c) Coding data or specimens and keeping the key to the code in a separate, locked drawer
   d) All of the above

6. If a researcher determines that his/her study poses no more than minimal risk as defined in 45 CFR 46, there is no need for the protocol to have IRB review and approval.
   a) True
   b) False
7. Because the expedited IRB review process is generally used for certain types of minimal risk research, it is less stringent than review by the full IRB.

a) True  
b) False

8. IRBs reviewing research in a different geographical location and/or cultural context have a responsibility to:

a) Obtain knowledge of the local context by talking to those who have traveled to the region 
b) Defer to an IRB that is situated within the local research context 
c) Ask specialists with direct knowledge of the local research context to participate in IRB discussions 
d) B or C  
e) A or C

Answer Key*:
1) 
2) 
3) 
4) 
5) 
6) 
7) 
8)

*Please enter the letter that corresponds to the answer you feel most appropriate for each question. You must provide answers to these questions for the assurance training to be complete. The correct answers will be provided when your certificate is issued.

"On my honor I have neither given nor received unauthorized information regarding this work, I have followed and will continue to observe all regulations regarding it, and I am unaware of any violation of the Honor Code by others."

__________________________________________

Name**

__________________________________________

Date of Completion of Training**

**Please type name and date, save and email the completed form to hsirb@davidson.edu. No handwritten signature is necessary.