Learning Objectives

• Identify essential elements for informed consent in research involving human subjects.

• Discuss issues commonly encountered by researchers in their effort to obtain and document informed consent.

• Describe a ‘best practice’ framework for obtaining and documenting informed consent.
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Introduction

- Historical Perspective
  - Four Periods and Paradigms of Research Oversight
- *Essential Elements* for informed consent
Historical perspective:
Researcher Paternalism Paradigm

- Dates: 1940 – early 1970s
- Triggering event(s): World War II
- Key protection: Researcher judgment
- Conception of subject: passive
- Conception of biomedical research: sharp distinction between care and research
- Underlying philosophy: Utilitarianism
- Highlighted ethical principle: Social value
Historical perspective: Regulatory Protectionism Paradigm

- Dates: 1970s – mid-1980s
- Triggering event(s): Jewish Chronic Disease Hospital; Beecher’s revelations; Tuskegee Syphilis Study
- Key protection: IRB review and individual informed consent
- Conception of subject: vulnerable party
- Underlying philosophy: Principalism
- Highlighted ethical principle: Independent review
Historical perspective: Participant Access Paradigm

- Dates: mid-1980s – mid-1990s
- Triggering event(s): AIDS epidemic; breast cancer movement
- Key protection: Individual autonomy
- Conception of subject: informed consumer
- Conception of biomedical research: clinical research is the best type of clinical care
- Underlying philosophy: Individual rights-based theory
- Highlighted ethical principle: Informed consent
Historical perspective: Community Partnership Paradigm

- Dates: mid-1990s - current
- Triggering event(s): genetic research within communities; international HIV/AIDS research
- Key protection: Host community collaboration
- Conception of subject: active participant in research
- Conception of biomedical research: continuous with clinical practice
- Underlying philosophy: Communitarianism
- Highlighted ethical principle: Collaborative partnership
Basic Regulatory Requirement for Informed Consent

• [With few exceptions], no investigator may involve a human being as a subject in research…unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative.

• 45 C.F.R. 46.116; 21 C.F.R. 50.20
Who is the Legally Authorized Representative?

• An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research.

• 45 C.F.R. 102(c); 21 C.F.R. 50.3(l)

• “Applicable law” means state or local law.

OHRP FAQs
Basic Regulatory Requirement for Informed Consent

• An investigator shall seek [informed] consent only under circumstances that provide the prospective subject or representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

• 45 C.F.R. 46.116; 21 C.F.R. 50.20
“Sufficient opportunity to consider....” Emergency Research?

• Consider study population, nature of research, timeline for making decision, possibility of coercion or undue influence.

• Also consider emergency exception (discussed later).

• OHRP FAQs
What is “Coercion” or “Undue Influence?”

• Coercion: Overt or implicit threat of harm (e.g., patient losing access to health services, or employee/student losing job or grade, if they decline to participate).

• Undue Influence: Offer of excessive or inappropriate reward or other overture (e.g., $$, student credits).

• OHRP FAQs
Basic Regulatory Requirement for Informed Consent

• The information that is given to the subject shall be in language understandable to the subject or to the representative.

• 45 C.F.R. 46.116; 21 C.F.R. 50.20

• Consider both non-English speakers and reading level/complexity of language.

• OHRP FAQs
Basic Regulatory Requirements for Informed Consent

• No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights….”

• 45 C.F.R. 46.116; 21 C.F.R. 50.20
“Exculpatory language?”

- Acceptable: “The hospital will not offer compensation or pay for medical treatment if you are injured in the study.”
- Exculpatory: “You waive your right to compensation or payment of medical expenses if you are injured in the study.”
- OHRP Guidance
What are the basic elements of informed consent?

• **DESCRIPTION**: A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental. 45 C.F.R. 46.116(a)(1); 21 C.F.R. 50.25(a)(1)
Description of Study

• How much is appropriate?
  • All in narrative format?
  • Charts/tables?
  • Bulleted lists?
• Is it necessary to describe every test?
• Standardized description of common procedures?
What are the basic elements of informed consent?

- **RISKS**: A description of any reasonably foreseeable risks or discomforts to the subject. 45 C.F.R. 46.116(a)(2); 21 C.F.R. 50.25(a)(2)

- **BENEFITS**: A description of the benefits to the subject or others which may reasonably be expected from the research. 45 C.F.R. 46.116(a)(3); 21 C.F.R. 50.25(a)(3)
Risks

• How to decide which risks are “reasonably foreseeable?”
  • Every risk that has been reported?
  • Only “significant” risks?
  • What about risks that have never occurred, but might be expected once more people receive intervention?
Benefits

• Consider likelihood of benefits:
  • Should any therapeutic benefit be listed for early phase trials?
  • Is description overly optimistic?
  • Is “increased monitoring” a benefit?
  • Is “helping future patients with your condition” a benefit?
What are the basic elements of informed consent?

- **ALTERNATIVES**: A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. 45 C.F.R. 46.116(a)(4); 21 C.F.R. 50.25(a)(4)

- **CONFIDENTIALITY**: A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. 45 C.F.R. 46.116(a)(5); 21 C.F.R. 50.25(a)(5) (also requires disclosure of possibility that FDA may inspect records)
Alternatives

• Must investigator list all possible alternatives?
• Is “doing nothing” or “waiting” an alternative?
What are the basic elements of informed consent?

• **COMPENSATION/TREATMENT**: For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and...where further information may be obtained. 45 C.F.R. 46.116(a)(6); 21 C.F.R. 50.25(a)(6)
What are the basic elements of informed consent?

- **CONTACTS**: An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject. 45 C.F.R. 46.116(a)(7); 21 C.F.R. 50.25(a)(7)
  - Note: Consider multiple contacts.
What are the basic elements of informed consent?

- VOLUNTARINESS: A statement that participation is voluntary, refusal to participate will involve no loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits. 45 C.F.R. 46.116(a)(8); 21 C.F.R. 50.25(a)(8)
What are the additional elements that may be provided for consent?

- **UNFORESEEABLE RISKS**: A statement that the research may involve risks to the subject (or embryo or fetus) which are currently unforeseeable. 45 C.F.R. 46.116(b)(1); 21 C.F.R. 50.25(b)(1)

- **INVOLUNTARY TERMINATION**: Circumstances under which the subject’s participation may be terminated by the investigator.... 45 C.F.R. 46.116(b)(2); 21 C.F.R. 50.25(b)(2)
What are the additional elements that may be provided for consent?

- **COSTS**: Any additional costs to the subject that may result from participation in the research. 45 C.F.R. 46.116(b)(3); 21 C.F.R. 50.25(b)(3)

- **EARLY WITHDRAWAL**: The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation…. 45 C.F.R. 46.116(b)(4); 21 C.F.R. 50.25(b)(4)
What are the additional elements that may be provided for consent?

- **NEW FINDINGS:** A statement that significant new findings developed during the course of the research that may affect the subject’s willingness to continue…will be provided.…
  45 C.F.R. 46.116(b)(5); 21 C.F.R. 50.25(b)(5)

- **NUMBERS:** The approximate number of subjects involved in the study. 45 C.F.R. 46.116(b)(6); 21 C.F.R. 50.25(b)(6)
When informed consent be waived or altered?

- IRB must find that:
  - The research involves no more than minimal risk to the subjects;
  - The waiver or alteration will not adversely affect the rights and welfare of the subjects;
When informed consent be waived or altered?

• Cont’d
  • The research could not practicably be carried out without the waiver or alteration; and
  • Whenever appropriate, subjects will be provided with additional pertinent information after participation. 45 C.F.R. 46.116(d)
When informed consent be waived or altered?

- Note: Waivers or alterations of informed consent for minimal risk studies are NOT permitted under FDA regulations. Even minimal risk research must include informed consent.
Written vs. verbal informed consent?

• Default: Informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject’s [LAR] at the time of consent. A copy shall be given to the person signing the form. 45 C.F.R. 46.117(a); 21 C.F.R. 50.27(a)
Written vs. verbal informed consent?

• Verbal permitted if “the research presents no more than minimal risk of harm…and involves no procedures for which written consent is normally required outside of the research context.” “[T]he IRB may require the investigator to provide subjects with a written statement regarding the research.” 45 C.F.R. 46.117(c)(2); 21 C.F.R. 56.109(c)(1), (d)
Written vs. verbal informed consent?

• Verbal also permitted (but **not** for FDA-regulated studies) if “the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from breach of confidentiality.” In those cases, subject gets to decide how to document. 45 C.F.R. 46.117(c)(1)
What about emergency research? Emergency Exception

- The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and [the study] is necessary to determine...safety and effectiveness.... 21 C.F.R. 50.24(a)(1)
  - Note: Ongoing debate about meaning of “unproven or unsatisfactory.”
What about emergency research? Emergency Exception

- Informed consent is not feasible because:
  - Subjects cannot give informed consent due to medical condition;
  - Intervention must start before informed consent is feasible; and
  - There is no reasonable way to identify prospectively potential subjects. 21 C.F.R. 50.24(a)(2)
What about emergency research?  
Emergency Exception

• Participation holds out the prospect of direct benefit because:
  • Subjects are in a life-threatening situation that needs intervention;
  • Animal and preclinical studies support the potential for direct benefit; and
  • Risks are reasonable in relation to the medical condition, standard therapy and anticipated benefits. 21 C.F.R. 50.24(a)(3)
What about emergency research? Emergency Exception

- The clinical investigation could not practicably be carried out without the waiver. 21 C.F.R. 50.24(a)(4)

- The study defines the therapeutic window, and the investigator attempts to contact LAR to obtain informed consent if possible. 21 C.F.R. 50.24(a)(5)
What about emergency research? Emergency Exception

• The IRB has approved the proposed consent procedures and a consent form to be used when obtaining informed consent is feasible. The IRB has approved a process and document to be used for allowing a family member to object to participation after enrollment. 21 C.F.R. 50.24(a)(6)
What about emergency research?  
Emergency Exception

- Additional protections:
  - Consultation with community from which subjects will be drawn;
  - Public disclosure of the study before commencement;
  - Public disclosure of results and subject demographics after the study;
What about emergency research?
Emergency Exception

• Additional protections (cont’d):
  • Establishment of independent data monitoring committee; and
  • If informed consent cannot be obtained, the investigator commits to attempting to contact a family member and providing the opportunity to object to the subject’s participation. 21 C.F.R. 50.24(a)(7)
What about emergency research? Emergency Exception

- Discussion of real study under emergency exception:
  - PolyHeme®
    - Are blood products “unproven or unsatisfactory?”
  - Was consultation and public disclosure adequate?
What about emergency research?  Emergency Exception

- Discussion of real study under emergency exception:
  - PolyHeme® (cont’d)
    - Grassley letter to DHHS – OHRP says study is “unethical”
  - WSJ articles
  - USA Today article: “God and PolyHeme® saved my life.”
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• Identify essential elements for informed consent in research involving human subjects.

• Discuss issues commonly encountered by researchers in their effort to obtain and document informed consent.

• Describe a ‘best practice’ framework for obtaining and documenting informed consent.
Summary of Issues Frequently Encountered

• Whether a particular amount or methodology for remuneration constitutes coercion or undue influence.

• Whether signatures on consent forms have to be dated or list the time.
Summary of Issues Frequently Encountered

• Whether the investigator has properly established the regulatory bases for waiving or altering some or all of the required elements of informed consent or parental permission. When is it not “practicable” to obtain informed consent.
Summary of Issues Frequently Encountered

• Disputes between Sponsor and IRB over consent form content.
  • Is the consent form a contract, and should it read as such?
  • Exculpatory language issue – frequently in research-related injury section.
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Participant informed about research and their rights

Participant is considered for study

Participant is approached for consent

Participant is informed of study and encouraged to ask questions

Participant declines participation

Participant is given time (if possible) to deliberate decision

Participant agrees to participate

Participant withdraws their consent

Frequent meetings with Participant regarding study progress

Completion of study procedure regarding participant

Data collection and analysis

Participant informed of study results

(Manning, 2000)
Tips on Informed Consent (OHRP)

• Informed consent is a process, not just a form
• Use the first person (e.g. “I understand that…”)
  • Use of scientific jargon and legalese is not appropriate.
• Describe the overall experience that will be encountered
Tips on Informed Consent (OHRP)

• Describe the benefits that subjects might reasonably expect to encounter
• Describe any alternatives to participating in the research
• The regulations insist that the subjects be told the extent to which their personally identifiable private information will be held in confidence
Tips on Informed Consent (OHRP)

• If research-related injury (i.e., physical, psychological, social, financial, or otherwise) is possible in research that is more than minimal risk..., an explanation must be given of whatever voluntary compensation and treatment will be provided

• The regulations prohibit waiving or appearing to waive any legal rights of subjects
The regulations provide for the identification of contact persons who would be knowledgeable to answer questions of subjects about the research, rights as a research subject, and research-related injuries. A single person is not likely to be appropriate to answer questions in all areas.
Tips on Informed Consent (OHRP)

• The statement regarding voluntary participation and the right to withdraw at any time can be taken almost verbatim from the regulations

• Don’t forget to ensure provision for appropriate additional requirements
Considerations for “Best Practices”

• Robust investigator education:
  • Emphasize informed consent as an ongoing process.
  • Reminder to use language understandable to subjects.

• Readability of consent forms:
  • Consider overall length and complex language.
  • AAMC project.
Considerations for “Best Practices”

• Informed consent monitoring program.
• Alternative methods of conveying information:
  • Web-based tutorial.
  • Video.
  • Just spending more time with subject. (JAMA article).
References

• General requirements for informed consent
  • http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116

• Documentation of informed consent
  • http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.117
References

• Research involving children
  • http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd

• OHRP Informed Consent Tips
  • http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm

• OHRP Informed Consent Checklist
  • http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm