Informed Consent: Human Subjects Protections and Research Operations

IRB Education Series
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Applying Ethical Principles

Respect for Persons: Autonomy
- Informed consent
- Voluntary participation
- Freedom to withdraw without penalty
- Protect privacy and confidentiality

Beneficence: “Do unto others…”
- Risks are minimized; Benefits are maximized
- Risks are justified by potential benefits
- Conflicts of interest are managed or eliminated

Justice: Distribute Risks and Benefits
- Protection of vulnerable populations
- Those who may benefit are not excluded
Informed Consent

45 CFR 46.116, 117

- Basic principle of respect for persons
- Dynamic *process*, not just a one time signing of an informed consent form (ICF)
  - Voluntary Involvement
  - Risks
  - Benefits
  - Procedures
  - Research-related Injury
  - Alternatives
  - Costs
  - Payment
  - Whom to Contact
Informed Consent
Required elements (45 CFR 46.116(a)(1-8))

(a)(1) “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”

“The purpose of this research study is to examine the safety and efficacy of [xxx] compared with placebo (a pill that looks like [xxx] but contains no active medication) in improving specific tests that indicate the degree of [zzz].”

“All patients will undergo a complete upper endoscopy under standard conscious sedation using a standard forward-viewing Olympus gastroscope. Patients will be monitored with standard protocols.”

“You’re invited to be in this study because you have…”

“If you take part in this study you’ll have the following done:…”
Informed Consent
Required elements (45 CFR 46.116(a)(1-8))

(a)(2) “A description of any reasonably foreseeable risks or discomforts to the subject”

“You could have a bad reaction if you are in this study.”
No additional information given.

“Subjects may experience diplopia, alopecia, myelosuppression…”

“You might have double vision, lose your hair, lose feeling in your hands and feet…”
(a)(3) “A description of any benefits to the subject or to others which may reasonably be expected from the research”

“A potential benefit of being in this study is you may experience a reduction in symptoms of your illness.”

“Your symptoms may get better if you take part in this study. But we can’t promise that they will.”
Informed Consent
Required elements (45 CFR 46.116(a)(1-8))

(a)(4) “A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject”

“There are no alternatives to being in this study.”

“An alternative is to not take part in this study.”
(a)(5) “A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained”

“We’ll keep your information private.”
No additional information given.

“Instead of using your name to identify you on study records and samples, we will create a code. With the code a number will identify you. Only [XXX] will be able to match your name to your number.”
Informed Consent
Required elements (45 CFR 46.116(a)(1-8))

(a)(6) “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 if so, what they consist of, or where further information may be obtained”

“There will be no means of remuneration for your involvement in this research.”

“You will not be paid for being in this study.”
Informed Consent
Required elements (45 CFR 46.116(a)(1-8))

(a)(7) “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”

“If you have any other questions, call someone on the research team.” No additional information given.

“At any time, you can ask us questions about this study. During the day you can call: [bullet point names and numbers]. At night, on weekends, or on holidays you can call: [bullet point names and numbers].”
Informed Consent
Required elements (45 CFR 46.116(a)(1-8))

(a)(8) “A statement that participation is voluntary, refusal to participate will involve no penalty or 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 to which the subject is otherwise entitled.”

“Your participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled. You may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.”

See Introduction language on ICF template on IRB website.
Informed Consent
Additional elements (45 CFR 46.116(b)(1-6))

- When appropriate, one or more of the following elements is also to be provided to the subject:

(b)(1) “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”

“There may be other risks that, at this time, we cannot predict if you will have or not.”

“[XXX] could cause these bad effects, or other bad effects that we don’t know about.”
(b)(2) “Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent”

“The study doctor may terminate you from this study if necessary.”

“If it is in your best interest, the study doctor may take you out of this study.”
Informed Consent
Additional elements (45 CFR 46.116(b)(1-6))

(b)(3) Any costs to the subject that may result from participation in the research

“There will be no extra costs to you.”
Implies that there are “other” costs.

“You would have the x-ray taken whether you take part in this study or not. Because of that, you or your insurance company will have to pay for the x-ray.”

or

“Since you will have an x-ray taken only because you are in this study, you will not have to pay for it.”
Informed Consent

Additional elements (45 CFR 46.116(b)(1-6))

(b)(4) “The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject”

This is very often completely missing from ICFs.
Informed Consent
Additional elements (45 CFR 46.116(b)(1-6))

(b)(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject”

“If we learn something important in this study we’ll tell you.”

“We’ll tell you about anything we learn in this study that might effect your choice to stay in this study.”
Informed Consent
Additional elements (45 CFR 46.116(b)(1-6))

(b)(6) “The approximate number of subjects involved in the study.”

“There will be as many subjects in this study as we need.”

“10 people will take part in this study at [Tufts NEMC/Tufts University Dental School.]”
Suggestions for Writing an ICF

• Proofread the ICF carefully
  • Eliminate redundancy
  • Eliminate technical terms and jargon
  • Write in short simple sentences (8th grade reading level or lower)
  • Verify all elements are present – create a checklist.

• Simplify
  • Use bullet points, charts, flow diagrams, a calendar of events, etc.

• Ensure that the ICF is accurate
  • Verify all procedures in protocol are in ICF.
Suggestions for Writing an ICF – What **NOT** to do.

- **DO NOT**...
  - Repeat things unnecessarily
  - Submit a sponsor’s ICF without carefully reading and reviewing it.
  - Assume that because the study has a sponsor, or the study is approved at another institution, the ICF is acceptable.
  - Rely on “readability statistics”
Proofread

• “Officials at the Food and Drug Administration… may inspect all records from this study due to their interest and support of this device.”

• “You must use an acceptable form of birth control while in this study. Abstinence is not an acceptable form of birth control.”

• “Risk of Pregnancy”
Consent Considerations – Operations and Process

• Open, easily understood communication process.
• Who will consent subjects to participate?
• When are subjects approached about participation?
  • Non-verbal cues
  • Ample time to think about study, ask questions
  • Need for re-consent?
    • Longitudinal study
    • Temporarily impaired competence
    • New procedures, safety information, etc.
• Location where study is discussed, consent obtained
  • Privacy
  • “White coat” effect
Additional Consent Considerations – Operations and Process

- Competence to provide “informed consent”
  - Impaired judgment does not mean exclusion
  - Rationale for including subjects with temporary or permanent impairment
  - Who will assess competence?
  - If subjects will be temporarily impaired, will re-consent be needed? When? Obtained by whom?
Additional Consent Considerations – Operations and Process

- Obtaining consent from an adult with temporary or permanent mental incapacity
- Such persons may only be enrolled if explicitly approved by the IRB (noted in the IRB Notice of Approval)
- “Legally authorized representative”
  - The IRB follows the clinical hierarchy of the hospital
    - Health care proxy/agent, upon proper invocation of the health care proxy
    - Spouse
    - Adult children
    - The patient’s parent
    - Adult siblings
Additional Factors

- Illness or disease state may be coercive
- Prospective subjects, research team members are potentially vulnerable to the humanity of disease
- Payment, free drug or device may be coercive
- Vulnerable subjects
  - Federal regulations
    - Pregnant Women, Human Fetuses and Neonates Involved in Research (45 CRF 46, Subpart B)†
    - Prisoners (45 CFR 46, Subpart C)†
    - Minors (45 CFR 46, Subpart D)†
  - State Law
    - Neonates (MGL Chapter 112, Section 12J)†

† May only be enrolled if explicitly approved by the IRB.
Enrollment of Minors

• Re-consent considerations
• If enrolled as a minor, at age 18 years consent from the subject is required.
  • Consent to participate in the study
  • Consent to tissue banking, if applicable
  • Consent to genetic testing, if applicable
  • If subjects cannot be located at age 18 years it must be documented that reasonable efforts to contact and inform the individual were made. Failure to obtain consent at age 18 years may hamper future research on banked samples, as at age 18 years subjects must consent to tissue banking/genetic testing or be able to withdraw their samples from being banked/tested.
Emancipated Minors

- Emancipated minors may only be enrolled if explicitly approved by the IRB (noted in the IRB Notice of Approval)
- A minor is considered emancipated and may consent to his/her own medical or dental care (except abortion or sterilization) at the time such care is sought, and the consent of the parent or guardian is not required, if the minor:
  - is married, widowed or divorced;
  - is the parent of a child;
  - is a member of any of the armed forces;
  - is pregnant or believes herself to be pregnant;
  - is living separate and apart from his/her parent or legal guardian and is managing his/her own financial affairs;
  - reasonably believes himself to be suffering from or to have come in contact with any disease defined as dangerous to the public health and is seeking treatment for that disease.
ICF Record Keeping

• Keep all pages of the signed ICF
• Keep the signed original in the study file
• Give a signed copy to the subject
• If applicable, send a signed copy to Medical Records
  • “back-up”
• Use version dates or numbers for quality control
• If an addendum ICF is generated, remember to reconsent all appropriate subjects
IRB Considerations: Phase I Studies
(metabolic & pharmacologic mechanisms; safety)

Pose a high level of risk due to “initial introduction” of the test article into a human; little or no human experience.

- Consent form issues (due to limited data and risks)
  - Rationale must be clearly stated (Purpose)
  - Risks must be stated as accurately as possible
  - Inclusion of animal data in consent form
  - Emphasis on monitoring and safety procedures
IRB Considerations: Phase II Studies
(controlled; preliminary effectiveness in subjects with the disease of interest)

Pose a high level of risk due to limited human experience.

- Consent form issues - All the concerns from Phase I studies, plus:
  - Potential efficacy must not be over-emphasized
  - Seeking of safety data must be included
  - Previous human experience should be stated.
IRB Considerations: Phase III Studies
(controlled & uncontrolled; increased human exposure to the test article; seek safety & effectiveness data for extrapolation to a larger population)

• Consent form issues - All the concerns from Phase I & II studies, plus:
  • Especially with an uncontrolled trial, alternatives must be clearly stated.
  • Availability of the “test article” at the conclusion of the subject’s participation may be an issue, especially if there is benefit.
IRB Considerations: Phase IV Studies
(long-term safety and efficacy data acquisition in a larger population)

• Consent form issues
  • The sponsor may not have created one!
Web Resources

- [http://www.hhs.gov/ohrp/irb/irb_guidebook.htm](http://www.hhs.gov/ohrp/irb/irb_guidebook.htm) (OHRP IRB Guidebook)
- [http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm](http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm) (HHS ICF checklist)
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