Informed Consent

Principles and Regulatory Requirements
What is Informed Consent?

- A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

(ICH, E6, 1997)
Main Goals of Informed Consent

- To inform participants about research
- To allow participants to evaluate whether they want to take part in the research and if the risks are acceptable to them
- To document the consent process
Not-So-Informed Consent

- **Nuremberg Code**
  - Trials of War Criminals, Nuremberg Military Tribunal, 1946 - 1949
  - Voluntary consent

- **Declaration of Helsinki**
  - World Medical Assembly (WMA) 1964
    - Ethical principles to provide guidance to physicians in medical research
    - Duty to promote and safeguard health

- **ICH Guidance E-6: Good Clinical Practices**
  - Ethical principles for treatment of subjects
Terms

- **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.
  
  21 CFR 50.3(l)

- **IRB – Institutional Review Board**
  - A group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such clinical research.

  21 CFR 50.3(i)
Terms

- **Test Article**
  - Any drug (including a biological product for human use), medical device for human use,…or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).
  
  21 CFR 50.3(j)

- **Minimal Risk**
  - 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.

  21 CFR 50.3(k)
Terms

- **Permission**
  - The agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation. Permission must be in compliance with 21 CFR 50, Subpart B, Informed Consent of Human Subjects and must include the elements of informed consent described in 50.25.
  
  21 CFR 50.3(r)

- **Assent**
  - A child’s affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent.

  21 CFR 50.3(n)

- **Children**
  - Persons who have not attained the legal age for consent to treatments or procedures involved in a clinical investigation under the applicable law of the jurisdiction in which the clinical investigation will be conducted.

  21 CFR 50.3(o)
No subjects may be involved in a clinical investigation without a signed, legally effective, informed consent form.

Sufficient time should be provided for subject to consider consent.

The possibility of coercion or undue influence should be minimized.
21 CFR 50.20
General Requirements for Informed Consent (cont’d)

- Informed consent language should be understandable.
- Informed consent cannot include language which waives the subject’s legal rights.
- Informed consent cannot release sponsor, investigator, or institution from liability for negligence.
21 CFR 50.25: Basic Elements of Informed Consent

- The following information should **always be included** in the informed consent form:
  - Statement that the study involves research, including the purpose of the research.
  - Expected duration of participation
  - Description of procedures to be followed
  - Identification of any procedures are experimental.
  - Description of any foreseeable risks or discomforts
  - Description of any benefits to the subject or others
  - Alternative procedures or treatments
    - “You may receive drug x outside of this study.”
21 CFR 50.25
Basic Elements of Informed Consent (cont’d)

- Confidentiality provisions and possibility that FDA or other regulatory agencies may review data
- Compensation for research related injury
- Available medical treatments
- Contact information for questions about the research, rights as a subject or to report research-related injury
- Participation is voluntary
- Participation can be discontinued at any time
21 CFR 50.25
Additional Elements of Informed Consent

- **May include:**
  - Potential risks which are unforeseeable (including possible risks to embryo or fetus if the subject becomes pregnant)
  - Termination of participation at the investigator’s discretion
  - Additional costs, if any, that the subject may incur
  - Consequences of subject’s decision to prematurely withdraw
  - New findings identified during research will be provided to subject
  - Number of subjects in study
When obtaining informed consent:
- Written form must be approved by the IRB, prior to use.
- Signed and dated by the subject or the subject’s legally authorized representative at the time of consent.
- Give a copy to the person signing the form.
State Laws for Informed Consent

- All 50 states require that subjects be informed of all alternative treatments and possible risks or complications before they are allowed to sign the Informed Consent Form.

- Extent of the amount of discussion is decided differently by each state.
What is the PI/designee’s job in the consent process?

- Provide to the research subject:
  - Complete information about the study (including revisions as new information becomes available)
  - Sufficient time to understand and ask questions about the information
- There should be no coercion or undue influence imposed upon the subject
- Make sure the informed consent process is documented (unless a waiver is granted)
- Not imply that the subject will be giving up any of their rights
- The investigator will not deny legal responsibility for issues related to negligence or include any other exculpatory language
Tips for Writing Informed Consent Forms

- 8th grade reading level:
  - Small words
  - Short sentences
  - Action verbs
- Layman’s terms
- Be direct
  - i.e. using “You”
- Outline timeframes, responsibilities and restrictions clearly

Do Not Try to Confuse the Subject!
You failed to obtain informed consent of each subject in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].

- You failed to obtain legally-effective informed consent from --- to whom you prescribed the investigational new drug...
  - Failing to obtain adequate informed consent jeopardizes the safety and welfare of enrolled subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.
  - Ten of sixteen subjects enrolled signed an outdated version of the informed consent documents, as opposed to a revised version which the IRB had approved prior to the date of signing.
    - Because these subjects were not given the opportunity to sign the revised informed consent documents, which contained new information about study procedures, they did not have sufficient opportunity to consider whether or not to continue their participation in the study, per 21 CFR 50.20.
The consent process, document and study related documents (e.g., survey instrument, medical release forms) must be presented in a language (preferably native) understandable to subjects.

If participants who do not speak English will be enrolled, translated documents should be available. The IRB must review & approve all foreign language versions of the consent documents.

The informed consent process must also be conducted in a language understandable to the participant and may require the use of a translator or sign language interpreter. In most cases, the translator may be a family member or friend of the participant, an employee of the institution or may be hired by the PI.

A translator must be available for the duration of the study to inform subjects of any new information should it become available as well as be available to address any questions the subject may have.
Barriers to informed consent

- Cognition/capacity (a lot of information vs. basic facts)
- Level of education (ability to assimilate information)
- Social/cultural values (trust in the medical system)
- Language
- Age (elderly and children)
- Environment (amount of time, pressure and privacy)
- Anxiety/fear (distracts and hampers understanding)
- Pain
- Influence of medications
- Quality of disclosed information
- Readability of informed consent form
Problems Observed in the Informed Consent Process

- Dates on the consent form do not match because the subject and the PI sign them on different dates.

- Lack of subject comprehension due to: low level literacy, foreign language, illicit drug and alcohol use, or prescribed drugs that may impair comprehension.

- Consent may be signed on the same date as study drug administration.

- The consent form signed was not the most recent IRB-approved version.
Problems Observed in the Informed Consent Process (cont’d)

- Subject was consented with the form for a different study
- Consent was not signed
- Copy of consent was not provided to subject (i.e. provision of copy not documented)
- In clinical trials, the consequence of receiving placebo and going untreated or undiagnosed are increasingly important. Subjects must understand what happens if they go untreated.
Documentation:

- Place a copy of the informed consent document with the medical records, research file, and also the regulatory binder (if necessary)
IRB may approve the clinical investigation without requiring informed consent if an independent physician finds:

- A subject is not able to consent due to a life-threatening situation
- Alternative methods of treatment are not available
- Scientific research is needed to determine safety and effectiveness of an intervention

Documentation of all activities is necessary!
Test articles *may* be used without informed consent, but:

- The investigator and a physician **not involved** in the study must certify each of the following in writing:
  - Life threatening situation; and
  - Inability to communicate with subject; and
  - Insufficient time; and
  - No alternative method or therapy.

Written certification or evaluation must be submitted to IRB within 5 working days after use of test article.
21 CFR 50.24
Exceptions for Emergency Research (cont’d)

• Intervention must be administered before consent from a legally authorized representative is feasible
• Subjects cannot be prospectively identified
• Anticipated direct benefit to the subject
• Trial cannot be conducted without the waiver

Documentation of all activities is necessary!
Two types of Consent Forms

- The subjects may sign either a:
  - Full consent form (that includes all the pertinent research information and the elements of informed consent), or
  - A short form (which contains a statement that the elements for informed consent were presented orally to the subject). IRB restrictions apply to the use of this form.
Past exceptions to informed consent requirement

- Emergency
- Mandatory donation
- Threat to community
- Dependents
- Contagious disease
- Criminal law enforcement
- Dangerousness
- Pregnancy

- Civil law discovery
- Impaired capacity
- Prison management
- Commitment
- Disorientation
- Preservation of life
- Life of Others
- Prevention of suicide
Assent

- In general, children under the age of two are considered too young to provide assent.
- Children between the ages of 2 and 6 should be read an oral script in simple language.
- Children between the ages of 7 and 12 should assent to research.
- Children over the age of 12 must assent to research, unless the IRB waives the requirement.
Obtaining Assent

- When the subject refuses to object, it does not count as an assent
- Rule of thumb:
  - Even if the parent gives permission, the child may still refuse to assent
  - If a child expresses assent, this does not override the parents refusal of permission

The assent discussion you have with the child is the most important!
Documentation of Assent

- The parent/legal guardian should sign the consent form.
- The child signs the assent along with the witness or person obtaining consent.
- Assent Form must be:
  - Age appropriate
  - Brief and specific
  - May include pictures and large type
21 CFR 50 Subpart D: Additional Safeguards for Children
Informed Consent Requirements

Parental Permission:

- Only one parent needs to provide written permission for the child to participate in research when research is:
  - Minimal risk, or
  - Greater than minimal risk and likely to directly benefit the child

- Both parents must provide written permission when research is:
  - Greater than minimal risk without direct benefit to the child

Exception: One parent may provide permission when one parent is deceased, incompetent, unavailable, or if only one parent has custody of the child.
Consent Requirements for Studies with a Certificate of Confidentiality

- A Certificate of Confidentiality (COC) protects the participant's confidentiality by protecting identifiable research records from subpoena. The certificate goes beyond the consent form in ensuring confidentiality and anonymity.
- Without the certificate, researchers can be required by a court-ordered subpoena to disclose research results (often as part of a criminal investigation of the participants).
- COCs are issued by the National Institutes of Health (NIH) and other Department of Health and Human Services (HHS) agencies.
  - They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in civil, criminal, administrative, legislative, or other proceedings, whether federal, state, or local.
- When in place, include language describing the COC requirements in the consent form.