

Informed Consent Process



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Introduction

The cornerstone of clinical research today is that of the informed consent process. History has taught both investigators and research participants many valuable lessons. Informed consent is more than just a document.

This module will define informed consent, its guiding principles, the document, and the process for obtaining consent. By the end of this module, the participant will be able to:

- Describe the guiding principles of the informed consent process.
- Describe the required elements of the informed consent document.
- Describe the appropriate procedures, including documentation, for consenting an adult, child, and a non-English speaking patient.
- Describe the difference between capacity and competency.
- List resources to assist with capacity and/or competency assessment.

What is Informed Consent (IC)

- Consent is having the capacity to agree for one's self to participate in a given situation (e.g., research) and, once the risks and benefits of participation are understood, agreeing to potential consequences.
- Informed consent (IC) is an ongoing process of communication and mutual understanding between a patient and investigator which is then demonstrated by the patient's voluntary agreement to enter a clinical trial.
- The patient's initial agreement is evidenced by signing an IC document.
- IC is **NOT** just a piece of paper, or a moment in time, or a contract.

Guiding Principles of IC

The guiding principles of the IC process are taken from the Nuremberg Code and the Belmont Report's ethical principle of respect for persons.

Nuremberg Code	Belmont Report
<ul style="list-style-type: none"> • Voluntary consent • Patient is free to stop at any time 	<ul style="list-style-type: none"> • People are autonomous agents and should be treated with respect • Informed consent must be freely and voluntarily given • Those of diminished capacity require additional protections

- Per the Belmont Report, the IC process contains the elements of:
 - Information sharing about the nature of the research
 - Comprehension of that information, and
 - Voluntary participation.

Beginning the IC Process

- The informed consent process begins with the development of recruitment materials and a recruitment plan.
- Both the Federal Regulations and GCP require that subject recruitment procedures, including advertisements, and other written information given to patients be reviewed and approved by the IRB before use.

[Click here to learn more about the IRB and review of recruitment materials](#)

IRB and Review of Recruitment Materials

- The IRB review of recruitment materials includes ensuring that there is:
 - No misleading text,
 - No claims of safety, efficacy, equivalence, or superiority,
 - No overemphasis of payment,
 - No overstatement of benefits.

Informed Consent Document

- The IC document is the written tool that is used by the Investigator to guide the discussion with a patient about a clinical trial.
 - Explains subject's rights of participation
 - Written in language understandable to the subject
 - Contains no [exculpatory language](#)
- When writing an IC document, there are certain elements that are required by the Federal Regulations.

8 Basic Elements of the IC Document...

(per 21 CFR 50 & 45 CFR 46)

- A statement disclosing that the study involves research including:
 - explanation of the purpose of the research
 - invitation to participate
 - expected duration of participation
 - description of procedures to be followed
 - identification of any procedures that are experimental (e.g., MRI that would not be done as part of standard of care, but for research only)
- Description of any foreseeable risks/discomforts
- Description of any benefits to patient or others
- Disclosure of any appropriate alternatives to study participation (e.g., standard comfort measures)

...8 Basic Elements of the IC Document

- How will the patient's confidentiality be maintained
- For research that involves more than minimal risk, an explanation regarding compensation if injury occurs, what that compensation is and how to obtain further information
- Contact persons for questions related to research and research subject's rights
- A statement regarding the voluntary nature of participation including that refusal to participate won't involve any penalty or loss of benefit to the patient

Waiver of Informed Consent for Minimal Risk Research Studies

The IRB can approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or may waive the requirement to obtain informed consent from some or all of the research subjects provided that each of the following criteria are met:

- 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;
- The research could not reasonably be carried out without the waiver or alteration; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

6 Additional Elements (per 21 CFR 50 and 45 CFR 46)

- The intervention or procedure may cause unforeseeable risks (e.g., risk to fetus if patient should become pregnant)
- Circumstance for termination of participation by the investigator (e.g., non-compliance with protocol's safety assessments, sponsor terminates an Investigational New Drug application)
- Additional costs to the patient from participation
- Consequences of the patient's decision to discontinue research participation
- Statement that the patient will be notified of significant new findings that may impact their decision to continue participation
- Approximate number of subjects

NCI IRB IC Template

- Each IRB will have an informed consent document template that you will need to use. The NCI IRB template is found on the CCR intranet site:

<https://ccrod.cancer.gov/confluence/display/CRCRO/Templates>

- When working on industry sponsored trials, multi-site trials or cooperative group trials, a sample IC document will be provided. This will need to be formatted using the IRB's template.

Writing an IC Document

- Writing an IC document so that a patient can understand it is a very challenging process. Approximately 40 million Americans are barely literate and another 45 million have very poor literacy skills. As for health literacy, slightly over 35% of in the U.S. are either at a basic or below basic level.
- Current practice is to write IC documents at an 8th grade reading level. However, recent research is suggesting that a 4th – 6th grade reading level is more appropriate for clinical trial consent documents.
- There are several types of readability tests used to establish the grade level of a document.
 - One of the easiest can be found when using Microsoft Word.
 - Microsoft Word uses the Flesch-Kincaid Grade level.

Challenges to Writing an IC Document

- Two major challenges when writing an IC document are related to
 - readability and
 - comprehension
- When writing an IC document always ask yourself, "Does the patient need this information in order to make an informed decision?"
- The next few pages will provide tips to improve both readability and comprehension.

Improving in Readability...

- State a clear purpose of the study
 - "The purpose of this study is to find the dose of an experimental medication...."
- Define all technical terms
 - A "catheter" is a small plastic tube....
- Use 2nd person singular (NOT 1st Person)
 - "You, the patient, will receive..."
- Give explicit information
 - "A small needle will be put just under your/your child's skin and a very small amount of fluid will be injected causing a little bump to rise up."

...Improving in Readability

- Use cause and effect statements when describing toxicities
 - "If the WBC level goes down, you have an increased risk of infection."
- Give concrete examples
 - You will need to have your blood drawn once a week on either Monday or Tuesday...."
- Highlight terms
 - "***Platelets*** are cells that help make clots in the blood."
- Create mental images
 - "Similar to the engine of a car, the heart..."

Tips to Increase Comprehension....

- Shorten words by removing unnecessary prefixes and suffixes, using simple synonyms
 - Average readable sentence length in American English is 17 words long
- Shorten sentence length
 - Sentences are considered too long if they contain more than 30 words
- If you read a sentence out loud and have to pause for a breath, the sentence needs punctuation or is too long!

....Tips to Increase Comprehension

- Remember organization and visual presentation:
 - Organize content under topical headings or short questions
 - Use the active voice and personalize the document to the patient
 - Minimum font size is 12 point
 - Quality of print and paper affects readability
 - Appropriate use of illustrations can improve comprehension

Signatures on the Document...

- Per the regulations (21 CFR 50.27, 45 CFR 46.117) , signature of participant/LAR is required
 - By signing the informed consent document, the participant/LAR is indicating his/her willingness to participate after receiving information regarding the study
- Per GCP guidelines (ICH GCP E6, 4.8), signature of witness is required
 - The witness attests that information explained accurately and understood by the subject/LAR AND that consent freely given.

...Signatures on the Document

- NIH [MAS 77-2](#) requires 2 additional signatures over that of the participant:
 - PI or designee obtaining the consent
 - Witness who attests only to the validity of the signature (i.e., that the research subject actually signed the consent), not to the validity or quality of consent.
 - Any adult other than the person obtaining or providing consent may be a witness to the signature.

Who Can Obtain the Consent?...

- Principle Investigator (PI)/Associate Investigator (AI)
- Individual need to be:
 - knowledgeable about informed consent process
 - knowledgeable about protocol
 - able to determine if the subject is well informed and making a free and uncoerced decision
 - able to identify and resolve outstanding questions
- Responsibility of PI to ensure an informed consent obtained and assess that subject gives voluntary consent, free of coercion or undue influence
- Review the CCR's [Policy](#) and SOP related to Informed Consent

...Who Can Obtain the Consent?

- If anyone other than an Investigator will be consenting a patient, the IRB must approve that process.
 - Often this is noted in the protocol, possibly in a human subject protection section, or this may be designated at the time of initial protocol submission to the IRB as part of the IRB process.
 - It is not typical for an IRB to approve a telephone consent process for an intervention trial, though this method may be acceptable for other types of clinical research.

Who Gives Consent/Assent for Research Participation?

- Informed consent is valid only with adults age ≥ 18
- Assent is obtained from children and adults who are unable to make their own decisions regarding research participation when possible.
 - Failure to object should not be construed as assent.
 - Assent is the affirmative agreement to participate in research.
- Individual should be competent to consent
- Individual should have the capacity to consent
- Surrogate "One appointed to act in place of another"
 - Legally Authorized Representative (LAR)
 - Guardian (court-appointed)
 - Durable Power of Attorney (DPA)
 - few states allow specific use of DPA for research

Capacity vs. Competence: What is the difference?

Capacity:

a one time clinical judgment of a client's ability to give informed consent

Competence:

the ability to understand legal rights and responsibilities and the possession of authority to make legal decisions

Participant Vulnerability and Factors Which May Compromise Capacity:

Panic
Delirium
Psychosis
Medical illness
Substance abuse
Cognitive difficulty
Dependency upon those who provide treatment

A cognitive impairment or a psychiatric condition doesn't automatically remove capacity.

Determining Capacity to Give Informed Consent:

- A subject must have capacity in order to provide informed consent
- The higher the risk in research, the higher the level of capacity required
- There is no single test of capacity
- There is an array of practices of documentation tools used, domains assessed and level of training

Facets of Capacity:

Capacity assessments are based on a modified MacCAT-CR. The four domains assessed are:

1. *understanding* of disclosed information about the nature of the research project and its procedures;
- 2) *appreciation* of the effects of research participation (or failure to participate) on subjects' own situation;
- 3) *reasoning* about participation; and
- 4) ability to communicate a *choice*

Appelbaum, PS & Grisso, T (2001). MacCAT-CR MacArthur Competence Assessment Tool for Clinical Research

Facets of Capacity

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 2. appreciation of the effects of research participation (or failure to participate) on subjects' own situation;
 3. reasoning about participation; and
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Appelbaum, PS & Grisso, T (2001). MacCAT-CR MacArthur Competence Assessment Tool for Clinical Research.

Who do you call for capacity assessments?

As per the NIH policy [MAS Policy 87-4](#) (*Research Involving Adults Who Are or May be Unable to Consent*), consultation regarding whether an individual is able to provide consent may be obtained by contacting the NIH Ability to Consent Assessment Team (ACAT) at either: 301-496-9675 or 301-496-2429.

When & How Will Consent be Obtained?

- Consent is to be obtained prior to any protocol specific procedures.
- Consent is typically done as a discussion using the IRB approved IC document as the guide.
- The setting should be quiet and private.
- The discussion needs to include a summary of the:
 - Purpose of the research
 - Procedures involved
 - Potential risks and benefit
 - Alternatives to participation

Steps in the IC Process

- **Step 1**
 - Investigator (or IRB approved designee) must explain the study to the patient verbally, providing all pertinent information (purpose, procedures, risks, benefits, alternatives to participation, etc.), and must allow the potential subject ample opportunity to ask questions.
- **Step Two**
 - A copy of consent should be given to the patient for further review prior to their making a decision. The patient should be given sufficient time to discuss the possibility of participating in trials with family, friends, and other physicians (e.g., patient's internist). "Sufficient time" can range from hours to days, depending on the type of trial.
- **Step Three**
 - After allowing the patient time to read the consent form, an Investigator (or IRB approved designee) should meet with the patient and answer any additional questions they may have.

Signing the IC Document

- It is important to stress the voluntariness of the patient's participation and that they may withdraw at any time. Using additional aids to highlight points can be helpful (e.g., if a tunneled catheter is needed for an intervention, have a sample available to show the patient).
- Once all questions have been answered to the patient's satisfaction, they will then be asked to sign the IC document.
 - **REMEMBER**, when a witness is required, instruct the patient to wait prior to signing so a witness can be available.
- After all signatures have been obtained:
 - original signed document will be filed in patient's medical record
 - copy of signed IC document is given to the patient
 - copy is kept by research team (e.g., copy filed in research shadow chart, or equivalent file).

Documentation of Informed Consent Process

- A specific statement (or note) should be written in the patient's medical record addressing the informed consent process. This should be done by all who discussed the clinical trial with the patient. Typically this will include a statement that:
 - A discussion occurred
 - All questions were reviewed and answered to patient's satisfaction
 - A copy of the signed IC document was given to the patient
- CRIS has an IC process template progress note

Children, Research and Assent

- Federal regulations state that parents and guardians must participate in an informed consent process just as they would do if they themselves were considering enrolling in a clinical trial.
- They must give legal permission for their child to enroll.
- This process must follow the guidelines established for the general requirements of informed consent as stated in the previous pages.

Assent...

- Assent is the child's affirmative agreement to participate in research
- Failure to object to participation should not be construed as assent
- IRB's may waive the requirement for assent (capacity-based waiver)
 - 45 CFR 46.408, 21 CFR 50.55
 - Insufficient capacity to participate in the decision
 - Direct benefit to the child

...Assent

- Age appropriateness needs to be considered including:
 - Maturity level
 - Psychological state
 - Disease
 - Level of comprehension and reasoning can be altered by:
 - Anxiety
 - Physical disturbances
 - Emotional disturbances
- The child's verbal assent needs to be indicated on the IC document (e.g., the parent's signature is also required next to a statement the child's did assent to participate. That means the parent would sign twice).

Assent Template

- The IRB determines if a separate assent document is required rather than a verbal assent
- Decision based on the expected level of comprehension
 - An Assent document is typically used if the child is over 14 years of age but consult with the IRB
- NCI IRB assent template is found at:
<https://ccrod.cancer.gov/confluence/display/CRCRO/Templates>

Non-English Speaking Subjects

- Federal regulations permit the use of a short form consent document when consenting a non-English speaking subject/LAR.
- The required informed consent elements have been presented to the patient/LAR orally, with a witness present.
- NIH Translation Office in the NIH Library offers fee-based translation services:
 - <http://nihlibrary.nih.gov/LibraryServices/Pages/Translations.aspx>

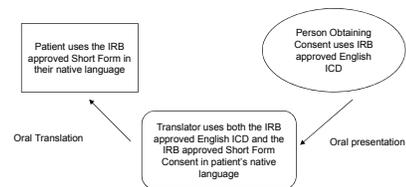
Consenting Non-English Speaking Subjects

The investigator must prepare:

- A consent form translated to a language understandable to the participant stating that the elements of informed consent required by regulations have been presented orally to the participant or the participant's legally authorized representative.
 - Translation should be done by a certified translator and back-translated into English.
 - Translation service (fee applies) available from the NIH Library.
- A written summary of what is to be said to the participant or the representative following the standard consent template.
 - This summary may be written in English.
 - Often this is the IRB approved English version of the IC document.
 - The IRB must approve both the consent form and the summary.

Process for Consenting Non-English Speaking Subjects

"Short Form" Consent Process (21 CFR 50.27, 46 CFR 46.117)



Overview:

"Short Form" Consent Process

Person obtaining consent must have:

1. Witness/Interpreter present during the consenting process/discussion and Q & A
 - Witness must be fluent in English and the language of the subject
 - Witness may serve as the interpreter
 - Recommended that the witness **not** be a family member or close personal friend of the subject (to help avoid coercion from the family and miscommunication of the consent process)
2. An English version of the current IRB approved consent form
3. A "short form" consent form translated into the subject's language, IRB approved
4. Presented all material outlined in the IRB approved consent orally to the interpreter who will then convey the information to the subject
 - Does not have to be read word for word
 - Person obtaining consent may present the information directly to the subject if he/she speaks the same language as the subject

Signatures on the Consent Documents "Short Form" Process

- "Short form", (21 CFR 50.27, 46 CFR 46.117), IRB approved
 - Signed by subject
 - Signed by witness/translator
- English version, IRB approved
 - Signed by investigator
 - Signed by witness/translator

NCI CCR Process...

- Notify IRB via iRIS prior to consenting non-English speaking subject – this includes screening protocols/consents
 - Upload both the English IRB-approved complete version and the IRB-approved non-English short form
- Wait for IRB approval, then proceed with informed consent using short form process
- Consent subject with an translator
 - Obtained through Social Work Department

....NCI CCR Process

- Document in subject's medical record just as with an English-speaking subject AND include the translator's name
- Copies of both signed consents given to subject
- IRB may request translated full English version if a few subjects have been through the "short form" process

Patients who understand English but are unable to read, write, or talk

- A person who speaks and understands English, but does not read and write, can be enrolled in a study by "making their mark" on the English IC document. The IRB should consider these persons as likely to be vulnerable to coercion and undue influence and should determine that appropriate additional safeguards are in place when enrollment of such persons is anticipated [see 21 CFR 56.111(b)].
- A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be enrolled in a study using an English IC document. The medical record document should include the method used for communication with the patient and the specific means by which the patient communicated agreement to participate in the study. An impartial witness must be present for the entire consent process and should sign and date the consent document.

IC for gene transfer studies

- For additional information related to informed consent and gene transfer studies, see the NIH Office of Biotechnology Activities (OBA)'s [guidance document](#).

Consent Considerations

- Informed consent should not be considered a one time signing of a document, but rather an ongoing dialogue between clinician and subject and a process that is revisited and re-evaluated through out the study for two reasons:
 - Nature of treatment may change with time
 - Subject's capacity to give informed consent may fluctuate

Re-consenting Study Subject: Signing a New IC Document

- Investigator is required to inform subject of new findings (e.g., toxicities) and to ensure that they are still willing to participate on clinical trial
 - Document this process in medical record, including willingness of subject to continue
- The IRB, or sponsor, may require that the subject sign the IRB approved updated IC document
 - *Never hurts to obtain anyway*
- For children who were *assented*, they will need to be *consented* when they become 18 years of age

Where to find IRB Approved IC/Assent Documents

All IC documents are posted by the NIH Clinical Center's Office of Protocol Support on the following website:

- NIH Clinical Research Studies Active Consent/Assent Documents search:
<http://www.cc.nih.gov/protocolconsents/search.html>
- Short forms (translations for approximately 30 languages) : <http://www.cc.nih.gov/protocolconsents/>

TIP: Bookmark both sites!

References

- Amdur, R., *Institutional Review Board: Member Handbook*. Boston, Jones and Bartlett Publisher, Inc. 2003.
- Appelbaum, P.S. & Grisso, T. *MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR)*. Sarasota, Fla, Professional Resource Press, 2001.
- Barfield, R. & Church, C. (2005). Informed consent in pediatric clinical trials. *Current Opinion in Pediatrics*, 17(1), 20-24.
- Flory, J. & Emanuel, E. (2004). Interventions to Improve Research Participants' Understanding in Informed Consent for Research: A Systematic Review. *JAMA*, 292, 1593-1601 .
- Emanuel, E., Crouch, R., Arras, J., Moreno, J., Grady, C. *Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary*. Baltimore: Johns Hopkins University Press. 2003.
- Joffe, S; Cook, EF; Cleary, PD; Clark, JW & Weeks, JC (2001). Quality of informed consent in cancer clinical trials: a cross-sectional survey. *The Lancet*. 358, 1772-1777.

Resources

- Department of Health and Human Services: Title 45 CFR 46: Protection of Human Subjects
- Food and Drugs: Title 21
21 CFR 50: Protection of Human Subjects
21 CFR 56: IRB function/operation
- Guidelines for Good Clinical Practice. International Conference on Harmonisation (ICH).

Evaluation

Please complete the [evaluation form](#) and fax to Elizabeth Ness at 301-496-9020.



For questions, please contact Elizabeth Ness
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