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Informed Consent

University of Virginia - IRB-HSR RESEARCHER BASIC COURSE

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Informed Consent

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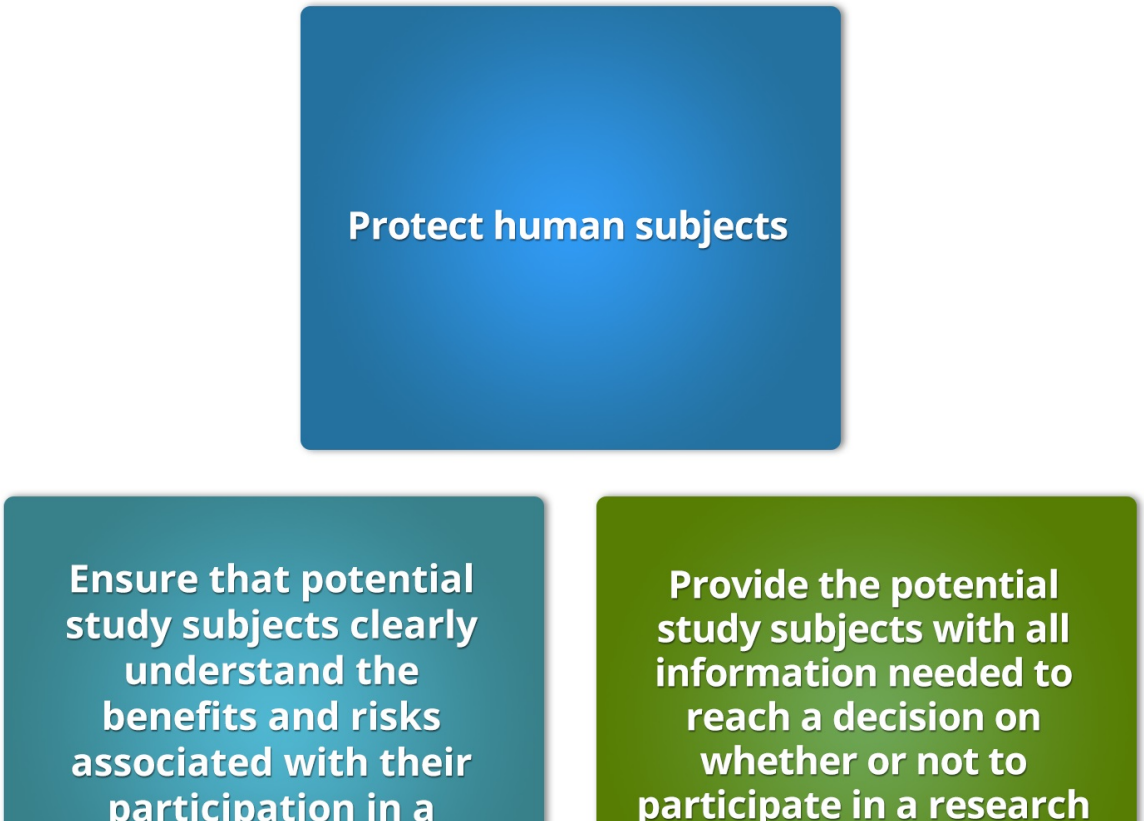
Introduction

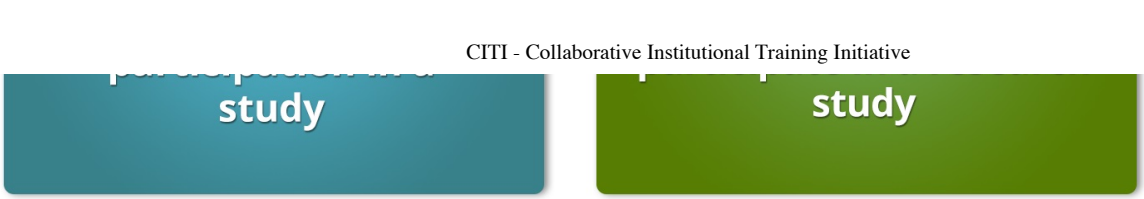
It is important to understand that informed consent is a process that begins with the recruitment and screening of a subject and the signing of the consent document and continues throughout the subject's involvement in the research and beyond study termination. Consent includes:

- Recruitment efforts encompassing the means of first creating awareness or contact and spanning everything from medical record review to advertisements and other recruitment materials.

- Providing specific information and answering questions about the study to subjects in a way that is understandable to them while giving subjects adequate time to consider participation.
- Obtaining the voluntary agreement of subjects to take part in the study. While the subject may agree to participate in the study, subjects may withdraw at any time. Part of the ongoing nature of the consent process is verifying the subject's continued interest in participating in the study.
- Making plans for the provision of new information to be shared with former subjects, even after the study ends.

There is consensus among researchers and Institutional Review Board (IRB) reviewers regarding the importance of informed consent. Informed consent is a demonstration of how researchers and those involved in human subjects research show respect to research subjects, and it is mandated by the U.S. Department of Health and Human Services (HHS) at 45 CFR 46 and the U.S. Food and Drug Administration (FDA) at 21 CFR 50. These regulations were developed to:





This module provides a basic understanding of informed consent and the process of obtaining informed consent.

Learning Objectives

By the end of this module, you should be able to:

- Describe the requirements for complying with informed consent regulations.
- Describe the process for obtaining informed consent.
- Discuss when subjects may be vulnerable to undue influence or coercion.
- Describe the regulations for waiving informed consent.

Key Terms

- **Broad Consent** is prospective consent for unspecified future research.
- **Key Information** is the brief description of the elements of informed consent presented at the beginning of a consent discussion.
- **Legally Authorized Representative (LAR)** means 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. If there is no applicable law addressing this issue, LAR means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research (Protection of Human Subjects 2018).
- **Vulnerable** means subjects in research studies vulnerable to the possibility of

- **Vulnerable** means subjects in research studies vulnerable to the possibility of coercion or undue influence.
- **Written or In Writing** refers to writing on a tangible medium (for example, paper) or in an electronic format (Protection of Human Subjects 2018).

Informed Consent Requirements

Consent should begin with key information, and then proceed with required elements and additional elements (as applicable) according to the regulation.

General Requirements

The framework for informed consent can be found at 45 CFR 46.116(a) (Protection of Human Subjects 2018) and 21 CFR 50.25(a) (Protection of Human Subjects 2015).

For some research, broad consent may be used as an alternative to informed consent for studies involving the storage, maintenance, and secondary research uses of identifiable private information and biospecimens.

Key Information Requirement

The HHS regulations require that informed consent begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject (or legally authorized representative [LAR]) in understanding the reasons why one might or might not participate in the research. The emphasis of the discussion is on subject (or LAR) comprehension and presenting information that a “reasonable person” would want to have in order to make an informed decision to participate, and an opportunity to discuss the information (Protection of Human Subjects 2018).

According to 46.116(b), legally appropriate informed consent will include the following

According to 46.116(b), legally appropriate informed consent will include the following elements:

1. A statement that the study involves research, an explanation of the research's purposes and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others that may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained (and for FDA-regulated research it should note the possibility that the FDA may inspect the records).
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.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a

research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.

8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
9. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:
    i. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
    ii. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Additional Requirements

In addition, if relevant to the research, legally effective informed consent will also include the following elements, outlined in 45 CFR 46.116(c):

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) that are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the researcher without regard to the subject's or legally authorized representative's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and

procedures for orderly termination of participation by the subject.

5. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.
7. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit.
8. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.
9. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (that is, sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

Broad Consent

Per HHS regulations at 46.116(d) (Protection of Human Subjects 2018), broad consent is an option in lieu of informed consent only with respect to the storage, maintenance, and secondary research use of identifiable private information and identifiable biospecimens. The information and biospecimens may have been collected for either research studies or non-research purposes.

Legally appropriate broad consent elements include required elements from informed consent, as well as additional broad consent elements. **Read more about broad consent required elements**.

The benefits of broad consent are still to be determined. The standard informed consent may still be used for the creation of biorepositories or research with

biospecimens.

Are Researchers Required to Use Broad Consent?

Researchers are never required to obtain informed consent through a broad consent process; it is an available optional procedure.

Instead of obtaining broad consent, a researcher may choose the following:

1. Conduct the research on non-identifiable information and non-identifiable biospecimens, and request that the IRB waive the requirement for additional prospective informed consent; or
2. Obtain consent for a specific study.

Even if the researcher wants to use the biospecimens with identifiers attached, the option still exists of asking an IRB to waive the requirement to obtain additional prospective informed consent instead of using broad consent (however, a strong justification would be required to support this request).

Read more about broad consent and IRB considerations.

Clinical Trials Consent Form Requirements

HHS defines a clinical trial as “a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes” (Protection of Human Subjects 2018).

FDA issued an additional requirement to the elements of informed consent that went

into effect in March 2012. When seeking informed consent for applicable clinical trials, as defined in 42 USC 282(j)(1)(A) (Director of National Institutes of Health 2012), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry

databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is (Protection of Human Subjects 2015):

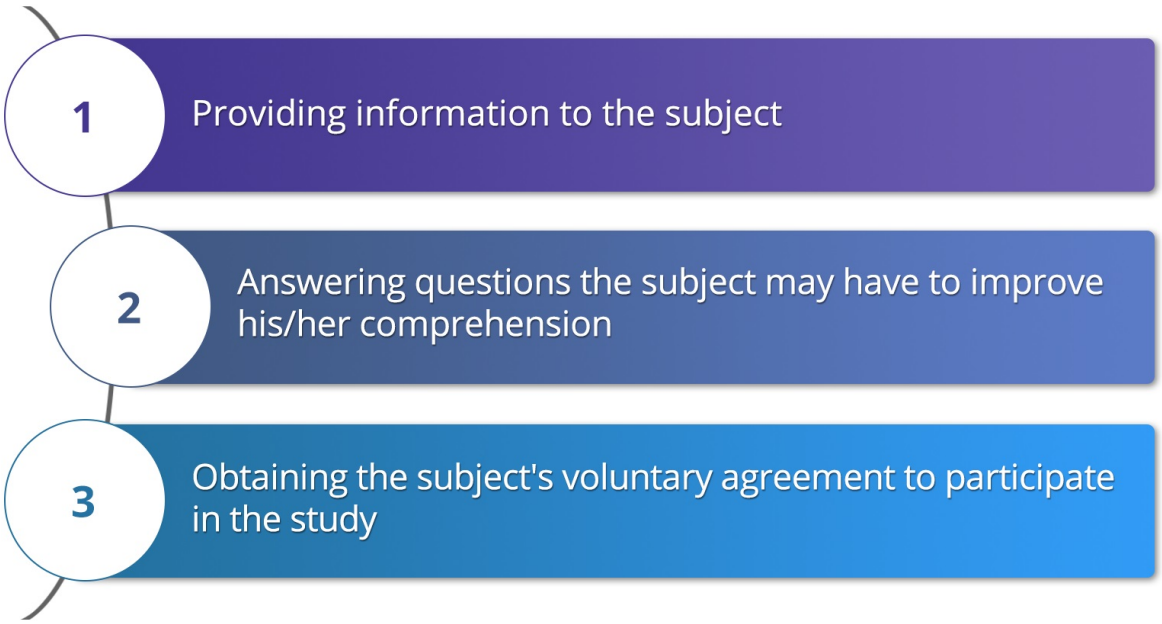
A description of this clinical trial will be available **http://www.ClinicalTrials.gov**, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

In February 2012, the FDA also issued **Guidance for Sponsors, Investigators, and Institutional Review Boards - Questions and Answers on Informed Consent Elements, 21 CFR 50.25(c)**.

If a research study qualifies as a clinical trial under the HHS definition and is subject to the Common Rule, there is an additional requirement to post the consent for to a publicly available federal website from 46.116(h). Until a special website is developed, or further guidance is provided, an option is posting the consent form for the trial to ClinicalTrials.gov or a docket folder on Regulations.gov (OHRP 2019).

Obtaining Informed Consent

Obtaining informed consent involves:



Providing Information

Guidelines for providing information include:

- Advertising may be the first information about research seen by subjects and is often used in recruitment. It cannot be coercive or make false promises or claims. The informed consent process is often conceptualized to begin at the recruitment stage. Additionally, some areas to consider with respect to recruitment include:
  - Laws, guidelines, or organizational policies that govern advertising for study subjects, particularly in multi-site research.
  - Whether compensation for study subjects is allowed where the research is proposed, and how it will be noted in recruitment materials.
  - What the "norms" for recruiting are in the particular location where recruitment

will occur and with the proposed population.

- Procedures to screen potential subjects for eligibility must protect the rights and welfare of prospective subjects.
- The information should be clearly communicated in an organized fashion and with understandable language, and allow for questions the subject may have.
- The information communicated should not use exculpatory language either in the written consent or in discussions about the research.

  No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence (Protection of Human Subjects 2018).

Improving Understanding

The regulations emphasize that consent must be understandable to the subject and provide information that would help the subject determine whether to participate. This includes providing sufficient detail about the research and presenting it in a way that facilitates understanding.

Guidelines for improving understanding include:

- Providing consent in a language that is understandable to the subject or subject's LAR.
- Providing non-English speaking subjects a translated informed consent document that is accurate (as determined by the IRB).
- If a translator is used, providing a written translation of the consent document is still required. Some IRBs allow use of a short form translation of the IRB consent document, see 45 CFR 4.117(b)(2). If a short form is used, the IRB must approve the

written summary of what is to be communicated to the subject (or LAR).

- Giving the subject enough time to think about participating in the research before giving consent.

The National Comprehensive Cancer Network (NCCN 2015) provides a free **online database** for researchers and IRB members that contains standardized lay language descriptions of risks and events associated with clinical research. This resource aims to help increase subject understanding by providing lay language terms approved by academic IRBs, which can be used in consent forms for clinical terms (for example, the term "reduced acuity" could be replaced with the lay term "blurry vision").

Obtaining Voluntary Agreement to Participate

Legally effective informed consent shall:

- Be obtained from the subject or the subject's LAR.
- Be obtained under circumstances that provide the subject with an opportunity to consider whether or not to participate and that minimize coercive influences. Coercive tactics (such as, inappropriate financial compensation or other rewards) cannot be used.
- Not include any language through which the subject is made to waive or appear to waive any legal rights or any language that releases the researcher, sponsor, or organization from liability for negligence.
- Subjects who are unable to read or write can "make their mark" on the informed consent document, as long as it is consistent with applicable state laws.

Special Challenges

There may be special challenges when consenting subjects who speak a different language or are from a different culture.

Language Issues

The consent process should be conducted in the language spoken by the subject and the consent form should be translated into that language. An IRB may require independent confirmation of the translation's accuracy. Subjects who are not literate in their language must have an interpreter present to explain the study to the subject and translate questions and answers between the subject and the person obtaining consent.

Cultural Issues

Issues other than literacy may affect comprehension. For example, in some cultures it may be considered rude to ask questions of a researcher, or rude to decline what is perceived of as a request for a favor. In these circumstances, the questions of who conducts the consent process and how it is explained become even more important.

Vulnerable Populations

The concept of subject vulnerability is important to research ethics and to regulatory

compliance. The regulations require that "when some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects" (Protection of Human Subjects 2018). The HHS and FDA regulations do not provide a definition of vulnerable populations or an explanation of the causes of vulnerability.

The FDA regulations at 21 CFR 56.111(b) provide the following list of examples:

- Children
- Prisoners
- Pregnant women
- Handicapped persons
- Mentally disabled persons
- Economically or educationally disadvantaged persons

HHS regulations differ from FDA regulations because their list does not include pregnant women or handicapped or mentally disabled persons, but does include “individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons” (Protection of Human Subjects 2018).

While vulnerability is not a term clearly defined in the regulations, thinking of vulnerability as a limitation on autonomy provides a valuable tool for considering whether there are sufficient safeguards in a given research project to protect the rights and welfare of these subjects.

Regulations for Waiving and Altering Informed Consent

Sometimes, under specific circumstances with IRB approval, informed consent can be waived.

HHS Regulations for Waivers and Alterations

HHS regulations at 45 CFR 46.116 (Protection of Human Subjects 2018) allow an IRB to waive or alter (change the requirements) for informed consent under the following circumstances:

1. Government projects
2. General waivers and alterations
3. Screening, recruiting, or determining eligibility

The IRB may not waive consent if an individual was asked to provide broad consent and refused. The IRB may not alter or omit any of the required elements of consent if broad consent was used.

Government Projects

A waiver or alteration of consent is allowed in research or demonstration project involving public benefit and service programs conducted by or subject to the approval of state or local officials and is meant to study/evaluate:

- Public benefit or service programs;
- Procedures for obtaining benefits or services under those programs;
- Possible changes in or alternatives to those programs or procedures;
- Possible changes in methods or levels of payment for benefits or services under those programs; and
- The research could not practicably be carried out without the waiver.

Common Rule General Waivers and Alterations

General waivers and alterations are permissible if the IRB determines that:

- The research involves no more than minimal risk to subjects;

- The research involves no more than minimal risk to subjects;
- The research could not practicably be carried out without the requested waiver or alteration;
- If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

It is important to note that the IRB cannot waive consent if an individual was asked to provide broad consent and refused.

Screening, Recruiting, or Determining Eligibility

An IRB may approve a research study in which a researcher will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject (or LAR), if either of the following conditions are met (Protection of Human Subjects 2018):

1. The researcher will obtain information through oral or written communication with the prospective subject or LAR.
2. The researcher will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

FDA Regulations for Exceptions from Informed Consent Requirements

FDA at 21 CFR 50.23 and 50.24 (Protection of Human Subjects 2015) provides exceptions to the requirement for informed consent under the following circumstances:

- In situations where requirements for exception from informed consent are met for emergency research.
- In life-threatening conditions involving an individual subject where requirements for an exception from informed consent are met and include documentation of all of the following:
    - The researcher, with the concurrence of another physician, believes the situation necessitates the use of a test article (an investigational drug, device, or biologic).
    - The subject and/or LAR is unable to communicate consent.
    - A LAR is "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" (Protection of Human Subjects 2015).
    - There is insufficient time to obtain consent.
    - No alternative exists that will provide an equal or better chance of saving the subject's life.

FDA Guidance on Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects

On 24 July 2017, the FDA issued guidance that they will not object if an IRB approves a waiver or alteration of consent for a no more than minimal risk clinical investigation if the IRB determines that (FDA 2017):

- The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k)or 56.102(i)) to subjects;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- The clinical investigation could not practicably be carried out without the waiver or alteration; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Waiver of Signed Consent/Use of Oral Consent

Signed consent may be waived and oral consent used under the circumstances discussed below.

FDA

FDA allows waiver of documented informed consent at 21 CFR 56.109(c)(1) (Institutional Review Boards 2015) when study participation presents minimal risk to the subject and the research involves no procedures requiring consent outside the context of participation in a research study. The IRB may require the researcher to provide the

subject with written materials about the research.

HHS

According to HHS at 45 CFR 46.117 (Protection of Human Subjects 2018), an IRB may allow waiver of a signed consent document under the following circumstances:

- The consent would be the only link between the research and subject and the principal risk to the subject would be due to a breach of confidentiality, and subjects will be asked if they want consent to be documented.
- Study participation presents minimal risk of harm to the subject and the research involves no procedures requiring consent outside the context of participation in a research study.
- If the subjects (or LARs) are members of a distinct cultural group or community in which signing forms is not the norm, that 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.

The researcher may be required by the IRB to provide a written summary about the research to the subject if these methods are used.

Is telephone consent from a LAR appropriate?

Verbal consent would mean that the consent form is not signed (no documentation obtained). The FDA and HHS regulations differ about verbal consent.

FDA

Under FDA regulations, verbal approval does not satisfy the 21 CFR 56.109(c) requirement for a signed consent document, as outlined in 21 CFR 50.27(a). However, according to **FDA (2016) guidance** it is acceptable to send the informed consent document to the LAR by fax and conduct the consent interview by telephone when the

LAR can read the consent as it is discussed. If the LAR agrees, he/she can sign the consent and return the signed document to the clinical researcher by fax.

HHS

Documentation of informed consent is required by 45 CFR 46 (Protection of Human Subjects 2018) unless a waiver of documentation is granted by the IRB. The regulations dictate that the signature must be from the subject or the LAR. HHS guidance regarding informed consent can be found at **OHRP's FAQs**. HHS does allow the exchange of consent information to take place face-to-face or by mail, telephone, fax, or video. An electronic format for the consent signature is also allowed.

Informed Consent

Electronic Informed Consent (eIC)

Electronic informed consent (eIC) can be used in a variety of ways during the consent process – from use of a video to demonstrate a study procedure, use of a tablet instead of a paper-based consent form, and use of electronic signatures. eIC is becoming a commonly accepted practice in clinical trials. However, federal regulations and Good Clinical Practice (GCP) guidelines (as applicable) about informed consent still apply.

Investigators and IRB members should be aware of both the benefits and challenges associated with the use of eIC to ensure the study's eIC consent process complies with regulations and GCP guidelines. The FDA and HHS issued joint guidance for IRBs, investigators, and sponsors on the use of electronic systems to obtain informed consent. The guidance (FDA and HHS 2016) focuses on the procedures to be followed when using eIC. The FDA and HHS guidance also makes it clear that the responsibility for obtaining the subject's consent ultimately lies with the investigator and cannot be delegated to an electronic system. HHS regulations also require that a written copy be given to the person signing the informed consent form. The copy could be in paper or an electronic format (Protection of Human Subjects 2018).

Summary

Before involving a subject in a clinical trial, the researcher is responsible for obtaining informed consent. According to regulations, such consent must be legally effective. Consent must be obtained under conditions that minimize the potential for undue influence or coercion. The process must also be documented according to regulatory requirements and the signature obtained only after the subject understands the information in the consent document and has had sufficient time to consider participation.

References

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Additional Resources

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