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Subject: Informed Consent
Division: IRB
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IRB Policy 108.1: INFORMED CONSENT

Policy

The IRB requires investigators to obtain the legally effective informed consent of each subject or their legally authorized representative. Informed consent is an on-going process between the subject and investigator which starts with the initial presentation of a research activity to a prospective subject, includes obtaining documented informed consent, and continues through the research activity until the subject ends his/her participation or the study closes.

Basic Elements

The informed consent form must embody the elements of informed consent contained in the HHS and/or FDA regulations. The IRB will review both the consent form and the process of informed consent to ensure its acceptability.

The basic elements of the consent process, as detailed below, include:

1. Full disclosure of the nature of the research and the subject's participation,
2. Adequate comprehension on the part of the potential subject, and
3. The subject's voluntary choice to participate.

In most research activities, an informed consent must be obtained by the investigator or his/her designee from each of the participants; or, in the case of those not able to give consent (e.g., children, mentally retarded), consent must be obtained from their guardians or legal representatives. A copy of the informed consent should be given to the person signing the form. The IRB must approve all consent documents and copies of such will be kept on file by the IRB.

An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative, and should be written at a sixth grade reading level. 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, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Language

In clear and non-technical language, subjects must be informed of:

1. The fact that the study is research.

2. The purposes of the research.

3. The expected duration of the subject's participation.

4. The procedures to be followed, whether there will be hospitalization to receive treatments, statements regarding medical procedures that will be performed and whether any are experimental. Include how many treatments will be given, how often and over what period of time.

5. Any reasonably foreseeable risks or discomforts.

6. The benefits to the subject or to others, which may reasonably be expected from the research.

7. Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

8. The extent to which confidentiality of data and privacy of subjects will be maintained. If the study is FDA regulated, include a statement that the FDA may inspect research records.

9. For research involving more than minimal risk, whether any medical treatments are available if injury occurs or whether there is any compensation for injury, and if so, what they consist of, or where further information may be obtained.

10. Whom to contact for answers to pertinent questions about the research, subjects' rights, and research-related injury to the subject. Include complete phone numbers and contact persons for various categories (about the specific study or about patient rights in general) of information that may become important to the subject at a later date. The contact for research subjects' rights should be the local IRB Chairperson.

11. The fact that participation is voluntary and that the subject may withdraw his or her consent at any time without penalty or loss of benefits.

The following additional elements of information shall also be provided to each subject, when appropriate:

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.

2. A statement that there are circumstances under which the subject may be terminated from participation by the investigator without the subject's consent such as when the subject does not follow the given instructions given to them.

3. A description of additional costs that may result from participation in the research, noting that some insurance carriers may not pay for care that is delivered in a research context.

4. An explanation of any consequences of a subject's voluntary withdrawal from the research and procedures for orderly termination of participation by the subject to protect the welfare of the subject.

5. A statement that the subject will be notified of any significant new findings developed during the course of the research which may influence the subject's willingness to continue participation.

6. Indicate the approximate number of subjects involved in the study.

7. If subjects will be paid more than $600 for their participation, the following paragraph should be included in the Reimbursement/Compensation section of the consent form:

   "If you complete this research study you will receive at least $600 for your participation. As a result, you must complete IRS Form W-9 before the research begins. This form contains your name, address, and social security number and will be submitted to Friends Research Institute's Accounting Office. At the end of each year FRI will issue an IRS Form 1099-Misc to you, and the Internal Revenue Service. This Form tells you and the Internal Revenue Service that a payment was made to you for your services, but it does not say that you were paid for participation in a research study. That information will remain confidential. You are responsible for paying any state, federal, Social Security or other taxes on the payments you receive."

8. For studies involving genetic research, the elements noted in IRB Policy 110.6 should be included in the consent form.

9. Permission to re-contact participants should be explicitly requested in the initial consent process if there is any possibility further information or samples will be sought, or to contact participants regarding additional studies. If the subject declines to grant permission, this request must be respected. The informed consent document should include an explanation of under what circumstances the subject would be re-contacted, and the options of accepting or declining. For example:

   CONTACT FOR FUTURE STUDIES
   Please check the appropriate box below and initial:
   ___ I agree to be contacted for future research studies
   ___ I do NOT agree to be contacted for future research studies

   If permission for re-contact was not given by the subject in the initial consent process, then IRB permission is required for any re-contact of subjects.

10. When the PI, Co-PI, or study doctor for a study may also be the participant's treating clinician, this potential conflict of interest should be disclosed to potential participants in the consent form. The following is an example of standard language that has been used in prior FRI approved consent forms:

    <u>Disclosure:</u>
    Your health care provider may be an investigator of this research protocol and, as an investigator, is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way associated with this research project. You are not under any obligation to participate in any research project offered by your doctor.

    To the extent possible, someone who is not directly involved in the treatment of a prospective participant should participate in the consent process.

11. When birth control is required for study participation the informed consent document should contain the following elements:

    a) The section describing study procedures should include among the screening procedures any pregnancy testing done for study purposes.
    b) The section on risks/discomforts should describe the risks to pregnant mothers, fetuses, and/or fertility of subjects as appropriate.
    c) The consent form should list acceptable methods of birth control (i.e., birth control pills, birth control patches, Depo-Provera, Norplant, an IUD, a diaphragm or condom with spermicide, abstinence), and instruct participants when they should start using them and for how long.
    d) The consent form should note if there is a possibility that the drug being studied may interact in a manner that makes the hormonal contraception less effective.
    e) The consent form should note that there is a risk that a participant or a participant's partner could still become pregnant even if s/he is using/have used a reliable method of birth control.
    f) The consent form should provide instructions for advising the PI if pregnancy is suspected.
    g) The Institute of Medicine recommends that pregnancy termination options be discussed (in a neutral, nonjudgmental way) as a part of the consent process in clinical trials that have unknown or foreseeable risks to potential offspring.
    h) The following is sample consent form language for requiring birth control (For Women):

        "If you are nursing an infant or you are pregnant now, you must not be in the study because we do not know how this drug could affect a fetus. Pregnancy tests will be done at screening, immediately prior to receiving the first dose of study drug, and every 4 weeks during your participation in this study. Pregnancy tests must be negative for you to enter and stay in the study.

        If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use a method *(two methods)* of birth control that works *(work)* well, like birth control pills, birth control patches, Depo-Provera, Norplant, an IUD, a diaphragm or condom with spermicide, or abstinence. You will have to do this the whole time you are in this study. There is a risk that you could still become pregnant even if you are using/have used a reliable method of birth control.

        If you become pregnant during the research study, please tell the investigator and your doctor immediately. If you are still receiving the study drug, you should stop taking it. We will still ask you to return for the rest of the evaluations, so that we can ask you information about your experiences with the drug."

    i) The following is sample consent form language for requiring birth control (For Men):

        "If you are a sexually active male and at risk of causing a pregnancy, you must be sure that your female partner(s) are using a method of birth control that works well, like birth control pills, birth control patches, Depo-Provera, Norplant, an IUD, or a diaphragm with spermicide, or you must use a condom with spermicide during sexual intercourse, or abstinence. You must do this the whole time you are in this study. A vasectomy **[***is/is not***]** an acceptable method of birth control for this study. There is a risk that your partner could still become pregnant even if you are using/have used a reliable method of birth control. If a sexual partner becomes pregnant during the research study, please tell the investigator and ask your partner to tell her doctor immediately."

12. When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), 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:

    "A description of this clinical trial will be available on*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."

General Guidelines

1. The use of the wording "I Understand" is inappropriate since most subjects will not understand the scientific and medical significance of all the statements. Also statements such as "This study has been fully explained to me" or "I fully understand the study" are inappropriate since the subjects cannot certify completeness of disclosure.

2. Use of the first person can be interpreted as suggestive, may be relied upon as a substitute for sufficient factual information, and can constitute coercive influence over a subject.

3. Use of scientific jargon and legalese is not appropriate. The reading level must be at or below 8th grade.

4. Use active voice rather than passive voice when possible (e.g., “the Investigators will ask you to…” instead of “you will be asked to…”).

5. No unsubstantiated claims of effectiveness or overly optimistic representations should be included.

6. Payments to the subjects should accrue as the study progresses and should not be an amount that could be considered coercive. The amount and schedule of payments should be submitted to the IRB for approval.

7. FDA explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's medical records when they pertain to the study.

8. Phrases such as "FDA has given permission" or "FDA has approved" should not be used.

9. FDA explicitly requires that consent forms be dated as well as signed by the subject or the subject's legally authorized representative. HHS regulations do not explicitly require consent forms to be dated. It is FRI IRB policy to require a signature date on consent documents, whether or not applicable federal regulations require a date.
    a. The subject or legally authorized representative must sign and date the consent form at the time of consenting process and only after all questions are answered and s/he agrees to participate in the study.
    b. The person who obtained consent from the subject or legally authorized representative must also sign and date the consent form. The signature cannot pre-date the subject’s or legally authorized representative’s signature.

10. For all research involving test articles regulated by the FDA, informed consent documents must include a statement that the purpose of the study includes evaluation of both the safety and the effectiveness of the test article. The consent form must also include a statement that the FDA has

access to the subject's medical records.

11. When the study subject population includes non-English speaking people, or if the Investigator has reason to believe the subject does not fully comprehend English, or if the consent interviews will be conducted in another language other than English, the IRB requires a translated consent document. A non-English speaking subject should receive a copy of the translated document.

12. A person who speaks and understands English, but does not read and write, can enroll by "marking their mark" on the consent document. An impartial witness should attest to the adequacy of the consent process and that the subject voluntarily agrees.

13. For research with children, children age 10 and above should sign assent to participate in the research; full consent is signed by the parent or legal guardian.

14. While most individuals assume that therapists and teachers act in the patient's or student's best interest, evidence has indicated that this assumption persists even if the subjects are told that the activity is research and will have no direct benefit for them. Therefore, special care must be taken in these settings to ensure that the potential subjects understand the nature of the research.

Documentation of Informed Consent

Informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative, and the person obtaining consent. A copy shall be given to the person signing the form.

The consent form may be either of the following:

1. A written consent document that embodies the elements of informed consent listed above. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

2. A short form written consent document stating that the required elements of informed consent have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the short form.

   Subjects who do not speak English: Where informed consent is documented using this short form procedure for non-English speaking subjects, the written informed consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. When this procedure is used with subjects who do not speak English, (i) the oral presentation and the short form written informed consent document should be in a language understandable to the subject; (ii) the approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject.

The IRB must receive all foreign language versions of the short form document as a condition of approval. Expedited review of these versions is acceptable if the convened full IRB has already approved the protocol, the full English language informed consent document, and the English version of the short form document.

With appropriate justification, the IRB may waive the documentation requirement for informed consent (45 CFR 46.117). Investigators contemplating such a request should discuss this with the IRB staff before submitting their protocol for approval.

An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

1. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern (note that FDA does NOT provide that an IRB may waive the requirement for signed consent when the principal risk is a breach of confidentiality because FDA does not regulate studies, which would fall into that category of research); or

2. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research. In this case, it is important for the research staff who obtain consent to write a progress note documenting the informed consent process. The progress note should be placed in the research record.(see Documentation of Informed Consent Process, page 11)

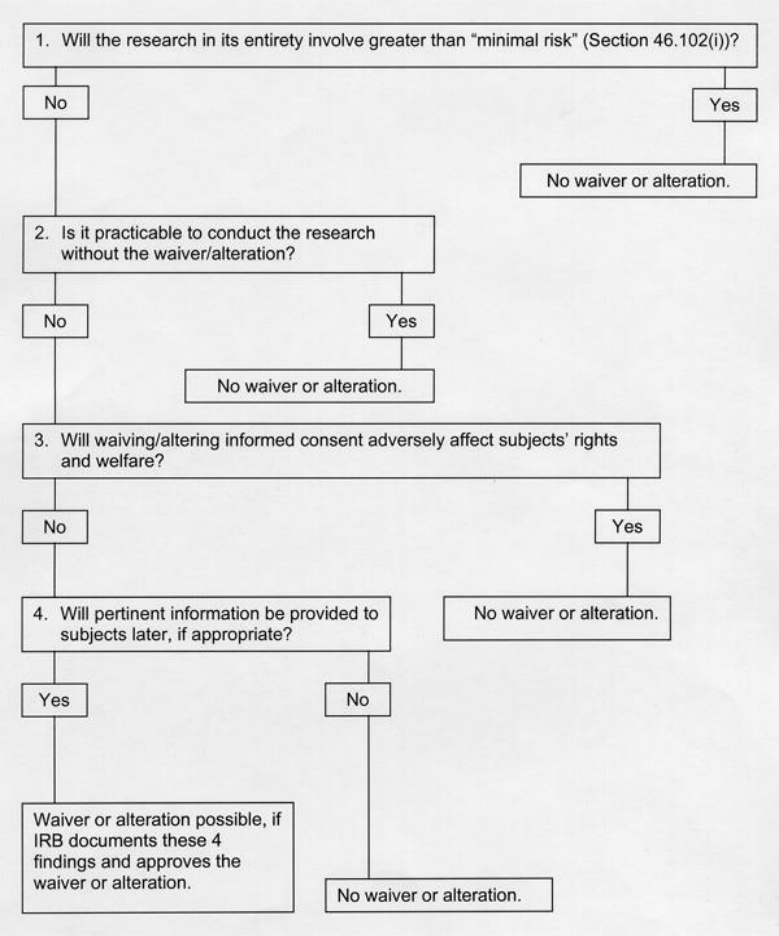
Informed Consent Alterations and Waivers

With appropriate justification, the IRB may waive the requirement for informed consent (45 CFR 46.116 (d)). Investigators contemplating such a request should discuss this with the IRB staff before submitting their protocol for approval.

The IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

1. The research involves no more than minimal risk to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The following OHRP Decision Chart will be used to help determine if the IRB can employ 45 CFR 46.116(d) to waive informed consent or alter informed consent requirements:



FDA provides for an exception from the informed consent requirements only in emergency situations. The provision is based on the Medical Device Amendments of 1976, but may be used in investigations involving drugs, devices, and other FDA regulated products in situations described in 20 CFR 50.23. FDA has no other provision for waiving or altering elements of informed consent under certain conditions, because the types of studies, which would qualify for such waivers are either not regulated by FDA.

FDA Exception From Informed Consent Requirement: Emergency Use

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject.
3. Time is not sufficient to obtain consent from the subject's legal representative.
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not

participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

FDA Exception From Informed Consent Requirement: Emergency Research

For FDA regulated studies, the informed consent requirements can only be waived if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following for emergency research:

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

2. Obtaining informed consent is not feasible because:
   a) The subjects will not be able to give their informed consent as a result of their medical condition;
   b) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
   c) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

3. Participation in the research holds out the prospect of direct benefit to the subjects because:
   a) Subjects are facing a life-threatening situation that necessitates intervention
   b) Appropriate animal and other pre-clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
   c) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

4. The clinical investigation could not practicably be carried out without the waiver.

5. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 21 CFR 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation.

7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
   a) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

b) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
c) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
d) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
e) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

The investigator (and ultimately the IRB) is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document, and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

Protocols involving an exception to the informed consent requirement must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists.

If the IRB determines that it cannot approve a clinical investigation because the investigation does not meet the above-mentioned criteria or because of other relevant ethical concerns, the IRB will document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA.

Cognitively Impaired Subjects

Studies involving subjects who are decisionally impaired may take place over extended periods. The IRB should consider whether periodic re-consenting of individuals should be required to ensure that a subject's continued involvement is voluntary. The IRB may require that Investigators re-consent subjects after taking into account the study's anticipated length and the condition of the individuals to be included (e.g., subjects with progressive neurological disorders). Additionally, the IRB should consider whether, and when, it should require a reassessment of decision-making capacity.

Use of Facsimile, Mail or Email to Document Informed Consent

In rare circumstances, depending upon the design of a study, the IRB may approve a process that allows the consent process be conducted telephonically and the consent document to be delivered by mail, facsimile, or email to the potential subject or the potential subject's legally authorized representative. Consent obtained by these methods must still comply with all regulatory requirements about the process, the consent elements, and documentation of consent unless the requirements are waived by the IRB. The subject or subject's legally authorized representative must return the signed and dated consent document to the person obtaining consent by mail, email or facsimile, before any research procedures may be implemented. All other applicable conditions for documentation of informed consent must also be met when using this procedure. For consent obtained by telephone, the researcher should describe a consent documentation process in the protocol as follows:

a. The subject or subject's legally authorized representative receives a copy of the consent documents in advance. For example, it could be mailed, emailed, or faxed.
b. The researcher conducts the interview process by telephone once the subject or legally authorized representative has received the consent form and can read the document as it is discussed. Sufficient time will be allowed for questions to be asked and answered, to ensure adequate comprehension of the consent information.
c. At the end of the consent discussion, an IRB-approved consent quiz will be administered to ensure subject's comprehension of the discussion.
d. If the subject agrees to participate, s/he signs and dates the consent document and returns it to the researcher via mail, email, or facsimile for the researcher's signature and date, before any research procedures begin.

With all telephone consents a progress note, signed and dated by the person obtaining consent, documenting the informed consent process must be placed in the subject's research record (see Documentation of Informed Consent Process).

Documentation of Informed Consent Process

It is considered good clinical practice for research staff to document the process of obtaining informed consent. This documentation in the form of a progress note should include; the name of the study, who was present during the consenting process, how the consent was obtained (i.e., telephonically, face-to-face), a statement that the study was explained to the subject or subject's representative, the subject's decision-making capacity (if impaired) at the time of consent, and whether the subject passed the consent quiz.

Applicable Regulations and Guidelines

45 CFR 46.116, 117
21 CFR 50, Subpart B
21 CFR 56.109(c)
FDA Information Sheet – A Guide to Informed Consent
OHRP Guidance Documents on Informed Consent