	University of Puerto Rico Medical Sciences Campus Human Research Subjects Protection Office	Effective: 9/1/2008
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INFORMED CONSENT AND CHILD ASSENT

Purpose:

To define the requirements for documentation of informed consent on human subject's research under UPR Medical Sciences Campus IRB jurisdiction.

Source:

45 CFR 46.116 and 117
45 CFR 46.408
21 CFR 50 Sub-part D

Applicability:

Research Investigators

Policy:

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representatives. Exceptions must be approved by the IRB.

It is a requirement that the investigator propose an assent plan as part of a research protocol that includes children as subjects. If the investigator believes that assent is not appropriate for children over the age of six, a waiver must be specifically requested, described, and justified in the protocol and subsequently approved by the IRB.

Procedures:

The consent process involves explaining a study to the prospective subject, ensuring that the individual has understood the information, giving that person adequate opportunity to consider all options, responding to their questions, and obtaining the individual's voluntary consent to participate. To be effective, the consent process must provide an opportunity for the investigator (or designee) and the individual to exchange information and ask questions--both at the time of recruitment and throughout that person's participation. It may involve the use of charts, models, video tapes and other audio visuals that may assist in communicating the procedures and processes that will be part of the study. For complex protocols, incorporation of diagrams and flow charts into the consent document itself is encouraged to improve the clarity and description of the research procedures and possible treatment assignments.

The consent document is a legal document containing sufficient information to allow the prospective research subject to make an informed decision about whether or not to participate in the research and ensures that adequate information is given to the subject in the process of obtaining consent. It is not intended to be a protection for the investigator and does not constitute any waiver of liability. The signed consent document provides documentation of a subject's consent to participate in a study.

The IRB must approve all consent documents to be used. Approval must also be obtained from the IRB for each modification made in the form thereafter, before instituting the change. The version of the consent document being used should match exactly with the version given final IRB approval in the protocol file. The IRB will stamp and date each approved version of the consent document. The investigators are encouraged to use the stamped and dated copies to assist them in assuring the appropriate version is in use. Guidelines for preparing a consent document follow.

Required Elements

Each of the following points must be covered in the consent document, except in cases where the point is irrelevant to the research:

(1) A statement that the study involves research, an explanation of the purpose of the research and why the subject is asked to take part.

(2) A description of procedures and identification of any procedures which are experimental. For example, the description of procedures should include the length and frequency of hospitalizations; number, frequency, and length of clinic visits; the total amount of time a subject should expect to devote to the study; names and types of medication; types and number of tests; amount of blood to be drawn; use of questionnaires; special diet; withholding of standard treatment; follow-up studies; and randomization, use of placebo, double-blind, or cross-over methods. In the case of patient subjects, state clearly which procedures are experimental and which procedures would be performed for medical reasons if the patient were not a research subject.

(3) A description of any reasonably foreseeable risks or discomforts to the subject, their frequency and severity. These may include drug side effects, hazards of procedures, withholding therapy of proven value, financial risk, loss of privacy, or possible detection of genetic predisposition to a disease. Describe what will be done to minimize risks, counteract side effects, and which side effects might be irreversible.

(4) A description of any benefits to the subject or to others which may reasonably be expected from participation along with a disclaimer that the investigator cannot guarantee there will be any benefit derived from taking part in the study.

(5) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. It is not necessary to provide a full account of the risks and benefits of standard alternative treatments in the consent document. In some cases, it may be appropriate to state that one reasonable alternative is to choose not to accept any therapy designed to produce cure or remission.

(6) A statement describing the extent to which confidentiality of records identifying the subject will be maintained. FDA and sponsor inspection of records in studies involving drugs and devices should be explained. The means of disclosure of information obtained during the study should be described, e.g., publication, entry in medical records, or transmission to another physician and assurance that publication will not lead to personal identification.

(7) An explanation that medical treatment is available if a research-related injury occurs. However, if a company or agency sponsoring

the research agrees to provide for additional treatment and/or monetary compensation for injuries, this should be included in the consent document.

(8) A statement about any costs for which the subject will be responsible and identification of any which are due solely to research. If the research activity will add substantially to the cost of patient care, state this clearly and specifically. It is important to explain to the subject/patient that they might have to pay more money for taking part in the study than they might pay for alternative treatments available and that their physician will discuss with them the costs of the treatment(s) offered through the study as compared to what other treatment might cost. The same applies when there is a disparity of costs between treatment arms (e.g. chemotherapy vs. bone marrow transplant) in the same study. Where applicable the subject should be informed that insurance carriers might not cover costs of research related procedures.

(9) A statement of the amount of compensation to be paid to the subject for participation in the research, approximately when they will receive the compensation and the manner in which it will be pro-rated in the event the subject does not complete the study.

(10) Identification including the full name(s) and 24-hour phone number(s) of the investigator(s) the subject may contact for answers to questions about the research and the research subject's rights, and whom to contact in the event the subject believes that he or she has sustained a research-related injury. This should include the Institutional Review Board as an agency prepared to identify the patients' rights.

(11) A statement that participation is voluntary and that the subject may refuse to participate or may withdraw from the research at any time without penalty or loss of benefits to which the subject is otherwise entitled. When appropriate, subjects should be assured that they will still receive standard treatment if they decide not to participate or to withdraw. They should also be assured that a decision not to participate will not adversely prejudice future interactions with the institution; this is particularly important when a dependent relationship exists between subject and investigator, such as physician-patient, employer-employee, or faculty student. If withdrawal may be dangerous to a subject (for example, abruptly stopping medication that should be tapered.), the danger must be explained and the subject should be told not to withdraw without first

discussing it with the investigator.

Additional Elements

The following additional elements of informed consent should be included when appropriate:

(1) A statement that the particular treatment or procedures may involve risks to the subject (or to the fetus, if the subject is or could become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's taking part may be terminated by the investigator.

(3) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue to take part will be provided to the subject.

(4) A statement that the investigational drug or device may not be available after the study period.

(5) A description of any plan to bank biological specimens or perform genetic analyses, including potential risks.

Format

- **Language**:

  The consent document should be worded in second or third person active tense (i.e. the participant…) and written in a language that the subject can be expected to understand (simple enough for a sixth grade student), and should not sound nor be coercive.

- **Two or More Consent Documents**:

  Sometimes is necessary to use two or more consent documents when procedures are to be performed on subgroups of subjects or when reasons for subject selection differ. The most common example of this situation is studies which involve both patients and normal subjects or a treated and a control population. If there is more than one consent document, place a label after the title indicating the subject population to which each is addressed.

- **Technical Elements**:

  At the top of the first page, the consent document should bear the title of the study, and the name of the institution. Pages should be numbered "Page 1 of 4", "Page 2 of 4", etc. At the end of the consent document there should be statements that the subject will be given a copy of the form to keep. Spaces should be provided for:

  a. The signature of the subject who consents to take part; or in the case of a minor, of the parent or guardian who consents on behalf of the subject and a line for the assent of the subject if age 6 or older;
  b. The signature of the individual who witnesses the subject's signature;
  c. The signature of the investigator or other approved person who enrolls the subject. The witness and the person enrolling the subject cannot be the same person. If someone other than an investigator is to obtain consent, IRB approval is necessary. Additionally, the signature of the witness attests only to the signature of the subject. Unless specifically identified and approved by the IRB, the witness does not act as a consent auditor.

Special Considerations

- Banking or Saving Biological Specimens or Creation of Permanent Cell Lines for Future Use

  When the research includes a plan to bank or save biological specimens for future use, the following must be addressed in the protocol and the consent form:

  (1) Provide an explanation regarding the purpose of obtaining/saving the sample(s) and indicate not only how they will be used in the immediate research effort, but state that samples will be stored or cell lines will be established from them with the intent to use them in other future research;

  (2) Describe how the subject's confidentiality and privacy will be safeguarded first in terms of how the physical samples and records will be handled in the lab and then how they will be handled when the research is presented or published;

(3) State who has control over the sample once it is stored in the laboratory. (The sample donor or the investigator) and where there exists a possibility of something being developed of commercial value, whether the sample donor may share in the expected profits;

(4) If the subject will be able to later withdraw his/her sample from further study, explain what subject should do to make this happen; give an estimate of the period of time the sample will be kept and used in future research;

(5) State whether subject will be given any results of the research being done now and or from future research done with their sample(s);

(6) State whether there is any possibility of third party access to information learned from the samples; and

(7) Clarify whether the subject would be contacted to ask for consent for future research endeavors using his/her specimen or to ask for additional information.

Genetic research

While much genetic research is in very early stages and would not yet have clinical implications, the eventual goal of most genetic research is to discover whether there is a genetic cause for a disease state or a genetic factor that could have treatment implications. DNA can be derived from many easily obtained biological specimens, so the risk associated with genetic research is NOT a physical risk. It is a social and psychological risk. Genetic information pertains to the most personal aspects of individuals' lives and may have implications for family members as well. The research protocol and the consent form must clearly state what type of information will be gained about the disease, its treatment, about the people who have the disease, about the individual tested, about their families and about their children. Subjects need to understand what the implications and what the potential consequences are of obtaining the information sought.

A subject might very well want to be part of the laudable effort to discover the gene that may cause Alzheimer. However, it may never occur to that subject that if it is determined he/she has the Alzheimer's' gene, it might

mean that he/she would likely develop the disease. Furthermore, if the results of the genetic research somehow become part of the subject's medical record and the medical record is later reviewed by the health insurance company, and the career. In pedigree studies, non-paternity and non-maternity may also be unexpectedly revealed, changing family relationships forever. Even when DNA is used in research without identifiers, some argue that DNA can never be truly anonymous since each person's DNA is unique, like a fingerprint.

Researchers planning genetic research must address the potential risks to the subjects and their loved ones, state how confidentiality will be safeguarded, indicate how results will be handled, specify the disposition of the biological specimen once the immediate research project is complete and clearly state what information will or will not be shared with the subject.

Deception

The IRB recognizes that in some cases, informing the subject of the hypothesis being tested may result in a biased response. Under these circumstances, the nature of some studies requires that the full purpose not be revealed to a subject until the study has been completed. Such intentional withholding of information may be permitted if the subject is informed that this is the case and agrees. Plans for when and how complete information will be shared with the subject should be disclosed in the consent document.

Pregnancy

If women of childbearing potential are included in a study and there are risks to the woman or fetus, the consent document should describe the test that will be done to determine whether the potential subject is pregnant, the need for contraceptive measures, and known risks of the research to a pregnant woman and fetus. If appropriate, the form should state recommendations about continuation of a pregnancy should the subject become pregnant, and who will bear financial responsibility for the termination of a pregnancy, should the subject and physician determine that this is the alternative of choice.

Screening Studies to Identify Eligible Subjects

If a procedure is to be performed solely for the purpose of identifying a population of research subjects, consent for the screening test and/or process is required. Often, it is appropriate for the screening to be presented in a separate consent document describing the screening procedure and stating that its purpose is to determine eligibility for participation in further studies. A separate consent document for the actual study would then be signed by individuals found to be eligible. In such situations, at the time the subject is enrolled for the screening procedures, the prospective subjects should be shown the document they will be asked to sign if they prove to meet the criteria for further study.

Distribution and Storage of Signed Consent Documents

A complete copy of the consent document must be given to each subject. A copy with original signatures must be retained in the investigator's file for a minimum of five years after completion of the study.

Guidelines for Subject Consent in Survey Research

Survey research involving the use of self-administered questionnaires and telephone and face-to-face interviews generally places subjects (respondents) at minimal risk. In addition to possible invasion of privacy and disruption of normal routine, the risks can include possible legal risks, possible inconvenience, embarrassment, and other kinds of psychological discomfort. Such risks may become more than minimal when sensitive information (such as sexually transmitted diseases, AIDS, alcohol and drug abuse) is requested.

Self-Administered Questionnaires

A cover letter containing the following information should accompany a self-administered questionnaire:

(1) An explanation of the purpose of the questionnaire

(2) An explanation of how and/or why the subject was asked to participate

(3) A statement of the amount of time the questionnaire will require

(4) A description of any stresses associated with sensitive information elicited

(5) A description of any benefits reasonably to be expected

(6) An offer to answer any inquiries concerning the questionnaire

(7) An instruction that the subject is free to refuse to fill out the questionnaire

(8) An assurance of confidentiality, including how confidentiality will be maintained.

In the instance that there will be no way of tracing respondents, return of the questionnaire to the investigator will be considered to be adequate informed consent provided the cover letter and contents of paragraph (1), above, accompanied the questionnaire.

Telephone and Face-To-Face Interviews

Whenever possible, a letter should precede an interview to inform the subject of the impending interview. The letter should contain the following information:

(1) An explanation of the purpose of the interview and the kinds of questions to be asked.

(2) An explanation of how and/or why the subject was chosen to participate in the study.

(3) A statement of the amount of time the interview will require.

(4) A description of any benefits reasonably to be expected

(5) An instruction that the subject is free to discontinue the interview at any time without prejudice.

(6) An assurance of confidentiality.

At the beginning of the interview, the information contained in the letter should be told to the subject again by the interviewer. Procedures for selection and training of interviewers should be described in the protocol. This should include the number of interviewers to be used, method(s) of recruitment, their familiarity with the community/population to be studied, the language in which the interview is to be conducted, and method of approaching subjects. In the instance of telephone interviews, and assuming that the information letter is part of the process, the oral consent of the interviewee to continue the interview will be considered to be informed consent. In the instance of face to face interviews, the informed consent document should be in writing. Informed consent should be obtained prior to the interview. The signatures of the subject, the interviewer, and the responsible investigator should be contained in the consent document. Like the letter and spoken introduction, the informed consent document should include all the information listed in items 1 through 6 above.

Waiver of Requirement for Signed Consent

The IRB may waive the requirement of **signed** consent in some circumstances, and may require instead that a written statement describing the research be given to the subject. (This does not mean that the consent process is waived).

Such a waiver may be given when one of the following conditions exists:

(1) The only record linking the subject and the research would be the consent document and the principal risk would be 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.

(2) 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.

Guardian Consent

Unless he/she is also a court appointed guardian or has durable power of attorney to consent for medical treatment, a "next-of-kin" usually cannot give consent for research on an adult subject. Permission for a child to take part in research must be obtained from a parent or legal guardian. Unless waived by the IRB, children who are capable of understanding their involvement in a study should be given the opportunity to assent to the research by signing the assent document in addition to their parents, having been informed of the nature of the project. Generally, age 7 is accepted as the age at which assent is sought. Emancipated minors (those under 21 years of age and married, or those for whom minority status has been court-removed) may consent on their own to take part in research. Although some minors may consent to certain types of medical treatment, there is no legal precedent that they, by themselves, may consent to take part in research.

Child Assent

Adequate provisions must be made for investigators soliciting the assent of children, when the children are capable of providing assent. The ages, maturity, and psychological state of the children involved should be taken into account. Generally, age 6 is accepted as the age children should give assent. If the procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, assent of the children is not a necessary condition for proceeding with the research.

***Definitions*:**

Adult is a person who has reached legal age. In Puerto Rico this is a person who has reached his/her 21st birthday. For research that includes subjects in other states or countries, other ages may apply. Federal regulations require research activities to comply not only with the Puerto Rico regulations but also with the laws of the state or country where research studies are performed.

Informed Consent is an individual's voluntary agreement, based upon adequate knowledge and understanding of the relevant information, to

participate in research either for themselves or for a minor for whom they have legal responsibility as the parent or legal guardian.

Permission means the agreement of the parent(s) or legally authorized guardian to the participation of a minor in research. This term is often used to emphasize that the parent is not the subject of the research. In this context permission has the same meaning as consent.

Assent means a child's written or verbal affirmative agreement to participate in research. Failure of a child to object to participation cannot be construed as assent.

Minor (Child) is a person, who has not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted.

Emancipated minor is a person under the legal age who, because of a special situation, has the legal rights of an adult. Situations that qualify a person as an emancipated minor vary by jurisdiction. In Puerto Rico, a married person under 21years of age is an emancipated minor; pregnancy outside of marriage does not emancipate a minor.

Parent generally means a child's biological or adoptive parent.
Foster parents are not authorized to give research consent.

Guardian is an individual, who is legally authorized under applicable state or local law, to oversee the care and management of the child and to consent on behalf of a child to general medical care.

Age guidelines for Assent

The following guidelines, based on the child's age, are usually followed by the IRB in determining assent requirements. Because of the many variables involved in research with children (age, maturity, cognitive ability, degree of study benefit to the child, health of the child, etc.), the guidelines listed below may not be applicable to a specific study and the investigator may propose a different plan. Also, the IRB has the option to require a different approach.

6 Years of Age or Younger, Verbal or Written Assent Is Usually Not Required

Consent is based on the permission of the parent or legal guardian, and no assent is required. A brief verbal explanation of the research procedure should be provided to the child.

Between The Ages of 7 to 13, a Separate Assent Form Is Required

In addition to the parents' consent form, a separate assent form is required for the child. It should be in language appropriate for children 7-13 years of age. The assent form should outline what is involved for the child, and emphasize the voluntary nature of the study. Depending on the research study, it will usually be one to two pages in length. An alternative to written assent is to use verbal assent. Verbal assent is obtained by reading the assent form to the child and obtaining the child's verbal agreement to participate in the study. Verbal assent needs to include the same content as written assent.

14 to 21 Years of Age, a Consent or Assent Form May Be Used

Children 14 to 21 years old may give assent by signing the Informed Consent Form that has been signed by the parent(s) or legal guardian. A separate assent form may also be used if the investigator believes it would better inform the child about the nature of the study. This would most likely apply to 14 or 15 year old subjects in very complex studies, or children with mild cognitive impairment.