CHAPTER 5

INFORMED CONSENT

Chapter Overview

I. THE PROCESS OF INFORMED CONSENT

Federal regulations stipulate that an investigator may not involve a person as a subject in a research study without obtaining legally effective informed consent from the person or the person's legally authorized representative (LAR). Consent to participate in research (informed consent) is an ongoing process which starts with the initial introduction of a research activity to a prospective subject and continues until the subject's participation is complete. The purpose of the consent process is to assure knowledgeable decision-making and voluntary participation.

The informed consent process is broader than the signing of the consent form. The process generally includes:

1. Bringing the research study to the attention of potential subjects;
2. Presentation and explanation of the study activities to the subject or their LAR;
3. Documentation of the informed consent process via a signed and dated written consent document;
4. Ongoing discussions between the research team and the subject regarding continued participation in the study;

and must:

5. Provide sufficient opportunity for the subject or their LAR to consider whether or not to participate or to withdraw at any time during the process;
6. Minimize the possibility of coercion, undue influence, or therapeutic misconception;
7. Be free of exculpatory language; and
8. Be in a language understandable to the subject or their LAR.

A. Initial Presentation of Research Study

The informed consent process must include all appropriate efforts to ensure that the subject genuinely understands his or her involvement in the research study. There must be sufficient time between the time the subject is initially contacted about the study and must decide whether or not to participate in the study. The amount of the time will vary on a case-by-case basis, depending on factors such as the specific nature of the research, the complexity of the information to be shared, and the population of potential subjects. The subject should be given an opportunity to take the consent form home for review when possible, or given time to consult with family, friends, personal physicians, religious advisors and/or others, either in person or by telephone.

Research subjects are rarely aware of what is involved with research activities prior to an initial presentation by the principal investigator or a member of the study team. In many cases, the prospective subject learns about the study during contact with their physician or the investigator. The presentation must not include any "leading" information about whether to participate in the particular study. Also, potential subjects must not feel rushed, coerced, or obligated to participate in any way.

Consent must not be solicited the same day as an **elective** procedure/therapy because the subject will not have had time to consider whether or not to participate and may be

distracted by the upcoming procedures or therapy (unless specific permission of the IRB is obtained). Several of the following measures may be taken by the research team to introduce research studies to prospective subjects in advance of participation to allow subjects sufficient time to consider study participation:

1. Providing referring physicians IRB-approved study-specific informational brochures or other recruitment materials to share with their patients;
2. Working with referring physicians' offices so that the research team nurses are notified in advance of a prospective subject;
3. Calling patients who have been introduced to the idea of participating in a research study several days earlier, so that research team members can answer questions.

Generally, the IRB expects that participation in a research study will not commence on the same day that the research study is introduced to the subject. **The IRB understands that this general rule may not be suitable for certain types of research (such as studies for which it is clinically necessary to initiate study procedures in a short period of time).** If an investigator wishes to introduce a research study to prospective subjects on the same day that research interventions will commence, then he or she must justify the request in the Adventist HealthCare Site Protocol.

For research studies that involve obtaining consent the same day that study participation begins, research team members must engage in a dialogue with prospective subjects and ensure the following:

1. The research project and consent form is thoroughly discussed with the subject;
2. The prospective subject is given the opportunity to privately discuss enrollment with family, friends, personal physicians, religious advisors and/or others, either in person or by telephone;
3. The prospective subject has access to aid devices that may help the subject read the consent form comfortably (i.e. eyeglasses, hearing aids);
4. The subject is given the opportunity to ask questions regarding research study participation; and
5. The subject is not rushed or coerced into participation.

B. Presentation of the Written Informed Consent Form

Written informed consent is required by federal and state regulations (unless waived by the IRB). Consent for research involving clinical procedures should be discussed during prior visits to the clinic, not on the day of the procedure. Whenever possible, potential subjects should be approached when they are rested, lucid, and able to use eyeglasses or hearing devices if they need them, and they may be accompanied by another person(s) if the potential subject so chooses. Also, patients should not be asked to sign hospital admission paperwork or hospital consent documents for clinically-indicated procedures at the same time as the presentation of the research consent form to avoid confusion between clinical care and research.

The principal investigator is ultimately responsible for ensuring that each research subject understands the information presented in the informed consent document. The principal investigator (or approved representative obtaining consent on behalf of the investigator) is responsible for explaining the study to the subject and for ensuring that the prospective subject reads the consent form (or that the form is read aloud to the prospective subject). After the prospective subject reads the consent form, the member of the study team must ask the subject if he or she understands the information contained in the form and has any questions about the study. Subjects should be able to explain what they are consenting to. It is the investigator's responsibility to ensure that the subject understands the research. Therefore, it is critical that the investigator not only answers questions, but also asks the subjects questions to confirm their understanding of their participation. This prompts subjects to think more carefully about participating in the research. Questions should be open-ended, evoking responses indicative of what the subject truly understands. Some examples of open-ended questions:

- Describe in your own words the purpose of the study.
- What are the possible risks? What is/are the possible benefit(s) to you of being in the study?
- So we can be sure you understand the research and what is expected of you, please explain what the research entails and what you will have to do.
- What additional information would you like to know?

The IRB has provided a comprehension tool (Appendix 1) as a resource.

If the individual decides to participate, he or she must sign the consent form and the investigator (or approved representative obtaining consent on behalf of the investigator) also must sign the form. In signing the consent form, the investigator is attesting that the research study has been discussed with and explained to the subject and/or the subject's LAR, and all questions have been answered.

C. Consent Monitoring

The IRB is authorized to observe (or have a third party observe) the consent process and the research itself (45 CFR 46.109(e); 21 CFR 56.109(f)). The IRB may require periodic or routine monitoring of the consent process with or without cause. Generally, the IRB will work with the investigator and the research team to carry out the consent monitoring in a way that minimizes any interference with the standard consent process.

D. Providing Ongoing Information to Subjects

Consent is an ongoing process involving the constant re-evaluation of current information and procedures. Subjects have the right to withdraw from a study at any time, and investigators are obligated to keep subjects apprised of issues related to their participation in the study. Any relevant new information generally must be reviewed by the IRB for approval and then shared with research subjects in a written form. The IRB may require subjects to sign an addendum to the consent form or to sign a revised consent form, as a way to ensure that the subjects have been informed of new information, as the regulations require that, when

appropriate, a "statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject" (45 CFR 46.116(b)(5); 21 CFR 50.25 (b)(5)). Thus, to ensure that consent remains legally effective, it is necessary to ensure that subjects still want to participate in the research if the protocol design or risks change, or if a substantial period of time elapses between the time consent was obtained and the study begins. It is possible that a subject may no longer be interested in participating, may no longer meet the eligibility criteria, may no longer find the risks acceptable, or may no longer have the time to complete all study-related activities. In general, periodic reiteration or affirmation of consent is a good idea, especially if the study takes place over a long period of time or is particularly complex.

Adverse events may occur during a research activity that would reasonably affect a subjects wish to continue participation. The IRB must be notified of these adverse events, and may require that the new information is shared with subjects as part of the continuing consent process. Additionally, information may arise which should be shared with previously enrolled subjects after completion of their participation in the study. To the extent possible, investigators should seek and obtain IRB review and approval prior to providing subjects with new research information. If prior review and approval is impossible, the investigator must provide the new research information to the IRB as soon as possible thereafter.

II. THE INFORMED CONSENT FORM

Once a prospective subject has been informed about a study and has expressed a willingness to participate, the investigator (or approved representative) must obtain consent using the current, IRB-approved informed consent form. Although a dated signature certifies the subject's willingness to participate, it is not equivalent to assuring that the subject understands the research. The IRB requires both the time and date to be recorded on the consent form in order to document that consent was obtained prior to participation. Federal regulations require that the subject be given a copy of the informed consent form (45 CFR 46.117(a); 21 CFR 50.27(a)). Adventist HealthCare policy also requires that subjects receive a copy of the signed and dated version of the consent form. Failure to do so is a violation of IRB approval.

An investigator may need to prepare more than one consent form, depending on the anticipated subject population. For example, a single trial may require a consent form for a competent adult subject, a permission form for the parent or guardian of a minor, and an assent form for a minor. Foreign-language versions of consent forms are generally required if people who do not speak English are to be enrolled. (A more detailed discussion of these issues is set forth later in this Chapter.)

A. Elements of the Informed Consent Form

Federal regulations mandate the inclusion of eight basic informed consent elements in consent forms and six additional informed consent elements, if applicable to the particular research (45 CFR 46.116; 21 CFR 50.25). These elements are identified in the Adventist HealthCare IRB Informed Consent Checklist. The IRB will review submitted informed consent forms using the Adventist HealthCare IRB Informed Consent Checklist. If any applicable elements are not adequately addressed in the submitted consent form, the IRB will return the proposed consent form to the investigator for revision. Each element, along with sample

language and instructions, is incorporated into the Adventist HealthCare Informed Consent Form.

Section headings should be used to clearly identify the required elements of informed consent. In most circumstances, the IRB expects the Adventist HealthCare informed consent form to be used as a template when preparing the informed consent document. Below is a summary discussion of the elements that should be set forth in the consent form. Note that the Adventist HealthCare informed consent form contains more specific instructions and required statements that are not identified in this policy.

1. First Page and Introduction

The first page of the consent form must clearly identify the names and contact numbers of the investigators conducting the trial and the name of the trial. The introduction paragraph should explain why the person was selected as a potential research participant and must clearly state that participation in the study is entirely voluntary and that the subject may choose not to participate. The subject's refusal to participate will not affect the quality of the medical care received, hurt the subject's relationship with the Hospital or doctors, or involve no penalty or loss of benefits to which the subject is otherwise entitled. If applicable, the form should state who is funding the research (e.g., name of the drug company, device manufacturer, or federal agency).

2. Research Statement (45 CFR 46.116(a)(1); 21 CFR 50.25(a)(1))

The informed consent form must include:

- a statement that the study involves research;
- an explanation of the purposes of the research;
- an explanation of the expected duration of subjects' participation;
- a description of the procedures involved; and
- identification of any procedures that are experimental.

The Adventist HealthCare Informed Consent Form divides these requirements into various sections, as follows:

a. Purpose of the Study (45 CFR 46.116(a)(1); 21 CFR 50.25(a)(1))

This section must provide a clear and accurate statement of the clinical purpose and objectives of the research and the reasons why the study is being conducted. If the study is a "pilot" study, "feasibility" study, or "Phase 1" drug study, this should be explained in the consent form. Some subjects are willing to participate in a study where the treatment or intervention has previously been studied in human subjects but are not willing to participate in a study when they will be among the first to receive the treatment or intervention.

b. Number of Subjects Involved (45 CFR 46.116(b)(6); 21 CFR 50.25(b)(6))

The consent form generally must identify the approximate number of subjects to be involved in the study at Adventist HealthCare as well as the number of subjects to be involved overall (e.g., study-wide).

c. Procedures (45 CFR 46.116(a)(1); 21 CFR 50.25(a)(1))

This section must clearly identify the procedures involved in the course of the research activity as well as the approximate duration of each activity required as part of the study. The difference between clinically-indicated procedures, protocol specific procedures, and experimental interventions must be explained in this section of the consent form. This requires a clear identification as to which drugs/devices/procedures are experimental or investigational and which are standard of care. The inclusion of a table with the information can be useful.

d. Duration of Involvement (45 CFR 46.116(a)(1); 21 CFR 50.25(a)(1))

The consent form must describe how long the subject will be involved in the study.

3. Risks and Discomforts

a. Potential Risks and Discomforts to Subject (45 CFR 46.116(a)(2), (b)(1); 21 CFR 50.25(a)(2), (b)(1))

This section must provide subjects with a clear description of any risks or discomforts that are reasonably anticipated during participation in the research. The risks associated solely with the study procedures or investigational drugs/devices must be identified separately from the risks of the services provided as standard care. In most cases, this section must include a statement that a particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if a female subject is or may become pregnant) which are currently unforeseeable.

In some cases it is appropriate to provide some probability of risk and severity of occurrence, risk prevention measures, reversibility and treatment. If applicable, this section must identify the reasonably foreseeable risks to an embryo or fetus, if a female subject is or may become pregnant or if the male can induce harm to an embryo or fetus through contact with a pregnant female.

b. Future Findings of Risks and Discomforts to Subject (45 CFR 46.116(b)(5); 21 CFR 50.25(b)(5))

The consent form must include a statement that significant new findings (including risks and discomforts) discovered during the course of the research that may affect a subject's willingness to continue participation will be provided to the subject. As discussed in section I.D. of this Chapter, investigators should, to the extent possible, seek and obtain IRB review and approval prior to providing subjects with new research information. The IRB will advise the principal investigator whether or not subjects should be asked to sign a revised consent form.

4. Required language for Research Involving Genetic Testing or the Collection of Genetic Information (to meet compliance with the Genetic Information Nondiscrimination Act of 2008 (GINA))

The IRB will consider the protections provided by GINA, particularly with respect to the following elements of informed consent that must be provided to subjects (unless an IRB has approved an alteration or waiver of these requirements in accordance with HHS regulations at 45 CFR 46.116(c) or (d)):

- A description of any reasonably foreseeable risks or discomforts to the subjects (45 CFR 46.116(a)(2)) from the collection of genetic information; and

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained (45 CFR 46.116(a)(5)).

The IRB must ensure that descriptions of the reasonably foreseeable risks of genetic research and any statements describing the extent to which confidentiality of records identifying the subject will be maintained do not overstate the protections provided by GINA (45 CFR 46.116(a)). OHRP recommends that for genetic research undergoing initial or continuing review, investigators and IRBs consider whether consent processes and documents should include language regarding the protections provided by GINA, and if so, ensure that such language accurately describes the impact of GINA on the risks and confidentiality protections for such research.

5. Anticipated Benefits (45 CFR 46.116(a)(3); 21 CFR 50.25(a)(3))

a. Anticipated Benefits to the Subject

This section must identify any benefits to subjects that reasonably may be expected as a result of participation in the research. Examples of direct benefit to the subject may include possible improvement of an illness or knowledge of value to the subject (e.g., results of a cardiac stress test, results of an educational test). If there is no reasonably foreseeable direct benefit to the subject, this should be stated. The consent form must not overstate the benefits, thereby creating an undue influence on subjects. Payment for participation is not considered a benefit of the research.

b. Anticipated Benefits to Society

This section must identify any benefits to society that may reasonably be expected as a result of the research. All research should have some underlying potential benefit to society (e.g., advancement of knowledge, health benefit to others).

6. Alternatives to Participation (45 CFR 46.116(a)(4); 21 CFR 50.25(a)(4))

All consent forms must indicate any therapeutic alternatives available to the subject in the non-research and/or research context that may be of reasonable benefit to the subject. Keep in mind that an alternative could be supportive care or “watchful waiting.”

7. Payment for Participation

This section must state whether the subject will be paid for participating in the study. Cash payments (if any) should be described in dollar amounts. Subjects also should be told when and in what form payment will be made and how much of the payment they will receive if they do not complete the research. Any credit for payment must be accrued by the subject as the study progresses and not be based on the subject completing the entire study. The nature, amount and method of payment or other remuneration must not constitute undue inducement to participate (e.g., the payment alone should not serve as sufficient inducement for the subject to volunteer). If reimbursement will be provided for costs of participation (e.g., parking fees, travel, lost time from work, baby-sitters), this information should be stated.

8. Possible Commercial Products

Investigators must inform subjects if any human materials (e.g., tumor tissue, bone marrow, blood) may be used to establish a commercially useful product, such as a cell line. Subjects also must be informed that they may not benefit (financially or medically) from the development of the cell line. If this section is inapplicable to a particular research study, it should be omitted from the consent form.

9. Costs and Financial Obligations (45 CFR 46.116(b)(3); 21 CFR 50.25(b)(3))

This section of the consent form must clearly state all financial obligations the subject may incur as a result of participation in the study, if any (e.g., physician fees, hospital charges, cost of medications, pharmacy dispensary charges, laboratory tests, post-treatment follow-up). In addition, this section also must indicate if drugs, devices, tests or services will be provided without charge. The consent form must disclose all reasonably foreseeable additional costs to the subject that may result from study participation (e.g., extended hospitalization, additional tests). Potential subjects should be advised that health insurance plans may not cover investigational treatments, procedures, drugs or devices.

If the researcher and/or the institution is paid for participating in the research study (e.g., by the sponsor or through a grant), this must be disclosed to the subject in the consent form. It is not necessary to disclose the specific details of the payment in the consent form.

10. Emergency Care and Compensation for Injury (45 CFR 46.116(a)(6); 21 CFR 50.25(a)(6))

For research involving more than minimal risk (i.e., most device and drug trials), the consent form must explain:

- If any compensation is available if the subject is injured; and
- If any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained.

The Adventist HealthCare Informed Consent Form contains examples of statements that may be used to satisfy this element, depending on the specific circumstances of Adventist

HealthCare's agreement with the sponsor in a particular trial. Also, the following text must be included in this section of the consent form: *"Please contact the investigator as soon as possible if you believe you are injured as a result of this study. You are not giving up any legal rights by signing this form."*

11. Privacy and Confidentiality (45 CFR 46.116(a)(5); 21 CFR 50.25(a)(5))

a. Confidentiality

This section should state that information obtained in connection with the research that could identify the subject will remain confidential and will be disclosed only with the subject's permission or as required by law. It should detail the measures taken to protect confidentiality, such as how specific records identifying the subject will be maintained.

Depending on the subject matter of the research, there may be limits to the investigator's promise of confidentiality to the subject. For example, if a subject reveals information about possible child or elder abuse, the investigator may be required to report such abuse to the authorities. Adequate notice to this effect should be included in the consent form if applicable.

b. HIPAA Privacy Rule Authorization

Under the HIPAA Privacy Rule, researchers generally must obtain a HIPAA-compliant authorization from each research subject permitting the researcher to use and disclose the subject's protected health information for the research study. The authorization must be written in easily understandable language and must contain specific core elements and required statements. See Chapter 9 on "Medical Research and the HIPAA Privacy Rule."

A HIPAA-compliant authorization may be incorporated into the informed consent form, or it may be presented to prospective subjects as a separate document. If it is incorporated, it should appear in the "Privacy and Confidentiality" section of the informed consent form. The Adventist HealthCare Informed Consent Form includes HIPAA-compliant authorization language to be used as a model.

12. Voluntary Participation and Withdrawal

a. Withdrawal by Subject (45 CFR 46.116(a)(8), (b)(4); 21 CFR 50.25(a)(8), (b)(4))

The consent form must include a clear statement that participation in the study is voluntary, 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 he or she is otherwise entitled. Also, this section must explain the consequences of a subject's decision to withdraw and the procedures for orderly withdrawal from the study.

b. Withdrawal by Investigator (45 CFR 46.116(b)(2); 21 CFR 50.25 (b)(2))

The consent form must indicate the anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent, if applicable.

13. Identification of Investigators and IRB Office (45 CFR 46.116(a)(7); 21 CFR 50.25(a)(7))

The consent form must explain who can be contacted for answers to questions about the research and research subjects' rights, and whom to contact in the event of a research related injury. Generally, questions about the research should be directed to the principal investigator (or appropriate members of the study team) and a 24-hour telephone number should be included in this section. The same contact information usually is appropriate in the event of a research related injury. Questions about the subject's rights as a research subject should be directed to the IRB Administrative office. The telephone number of this office should be provided.

14. Additional Clinical Trial Information for Subjects (21 CFR 50.25(c))

The consent form for FDA-regulated drug, biologics, and device clinical trials must include a statement that clinical trial information will be entered into a databank. The databank refers to the clinical trial registry databank maintained by the National Institutes of Health/National Library of Medicine. The required statement is as follows:

"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."

B. Readability of the Consent Form

The informed consent form must be written using language understandable to the subject (45 CFR 46.116; 21 CFR 50.25). While the IRB reviews consent forms to ensure that they are understandable to the potential subject population, the study sponsor, research team, and the IRB have a shared responsibility to ensure that the consent form meets readability standards. Consent forms should avoid (or define) medical jargon or terminology and adjust for educational background and age of the subject population. In most circumstances, the IRB expects that consent forms be written at no higher than an eighth grade reading level. Language copied directly from a protocol is not appropriate. Generally, consent forms should be written in the second person (e.g., "Your participation in this study is entirely voluntary") and should be written as if the author and the subject are engaging in a dialogue.

Prior to submitting a consent form to the IRB for its review, the investigator should determine the Flesch-Kincaid grade level of the consent form using Microsoft Word's built-in readability assessment.

There are various online resources for investigators to use to help simplify the language in consent forms. Several of these resources are identified below.

- http://www.med.umich.edu/irbmed/guidance/guide.htm
- http://www.irb.ufl.edu/glossary.htm
- http://www.plainlanguage.gov
- http://humansubjects.stanford.edu/general/glossary.html

C. Obstacles to Obtaining Informed Consent

1. Language Barriers (45 CFR 46.116, 46.117; 21 CFR 50.25, 50.27)

Informed consent information must be presented "in language understandable to the subject," and consent must be documented in writing, unless the requirement is waived by the reviewing IRB. These requirements present particular challenges when a potential subject is not fluent in English. Historically, some institutions have attempted to avoid this issue by excluding those potential subjects who do not speak English. While this may seem practical for the researchers, this apparent solution is contrary to the regulatory requirement that IRBs ensure the equitable selection of subjects and to the government's position that minority groups should be represented in research unless their exclusion is justified by the research protocol itself.

There are two ways an investigator may obtain consent from a non-English speaking subject: either by using (a) a translated version of the IRB-approved informed consent form, or (b) a qualified interpreter to orally interpret the consent form in conjunction with a short form written consent document (Short Form), in a language understandable to the subject (discussed in more detail below). When using either method, a copy of any translated consent materials must be approved by the IRB prior to implementation. If it is reasonable to expect that the subject population will be fluent in English, translated documents need not be submitted at the time of initial IRB review. However, once a non-English speaking prospective subject is identified, translated documents must be submitted to the IRB for expedited review prior to obtaining consent from the prospective subject. Expedited review of these documents may be acceptable if the protocol, the full English language informed consent document, and (if applicable) the English version of the short form have already been approved by the convened IRB.

a. Translated Consent Forms

When it is likely that research will include non-English speaking subjects, researchers should prepare both English-language and translated consent forms. The IRB encourages the use of a full informed consent form translated into the subject's language when a non-English speaking population is targeted. The IRB requires submission of: (a) a certification statement of both the forward- and back- translations, (b) a statement about the expertise of the translator/translation service, and (c) a back-translation of the forward translation submitted by the researchers.

b. Short Forms

As an alternative to translated informed consent forms, the IRB may approve an oral presentation of the informed consent form information in conjunction with a short form (stating that the elements of consent have been presented orally).

The IRB *stresses* that short forms *cannot* be used as a substitute for a translated informed consent form when the primary population of a study will be non-English speakers. In that instance, fully translated informed consent forms should be provided for IRB review with an English language version.

The short form may be approved by the IRB on a protocol-by-protocol basis, for use with subjects who are not English-speaking. The IRB will consider the study complexity and the amount and duration of subject involvement when determining if use of the short form is appropriate and can be approved. If a non-English speaking subject is initially consented for a study using an approved short form, to the extent the study includes ongoing interventions or interactions with the participant, the research team will assess the feasibility of translating the full IRB-approved English consent into the subject's language whenever possible.

The assistance of an interpreter and the presence and signature of a witness are required when using the short form.

1. Who can be the translator/interpreter?

    a. Preferably, a hospital interpreter who has completed the Level 2 Qualified Bilingual Staff certification offered by the Center on Health Disparities should be used whenever possible.

    b. If a member of the study staff speaks the subject's language, the staff member can act as the interpreter and can obtain consent (if designated to do so), but should **not** also act as the witness.

    c. A family member of the subject **cannot** act as an interpreter.

When using the short form, there must be an impartial witness to the oral presentation, who should be fluent in both English and the language of the subject. An impartial witness is someone who is independent of the trial and who cannot be unduly influenced by people involved in the trial.

2. Who can serve as a witness?

    a. The witness may be staff, interpreter or other person.

    b. When the person obtaining consent is assisted by a interpreter, the interpreter may act as the witness (as permitted by OHRP).

c. Before starting the consent process, verify whether the interpreter will also be able to serve as a witness - if not, another person will need to act as the witness.

d. A member of the study staff acting as interpreter and obtaining consent should **not** also act as witness.

In order to use the short form, the following must be submitted for IRB review and approval:

- A justification for the use of the short form;
- A summary of what will be presented to the subject (or LAR) or the informed consent document in English;
- Text of the short form, in English and in translated language;
- Certification (by the translation service) statement of the forward- and back-translation of the English short form to the translated language, and back to English. The IRB recommends that translators have the necessary experience to provide these translations. The translator must provide a signed translator certification statement. Please see the sample of the statement below:

  Sample Translator Certification:

  I hereby swear that I am fluent in English and (name of language) and that I have, to the best of my knowledge and belief, made a true and complete translation from English to (name of language) of the (Name of Document, i.e. Research Subject Information and Consent Form; Advertisement) this (insert date).

  (Signature of Translator)

  Name of Certification (ATA, DSHS)_____

  Certified by the State of_____

  Certificate No._____

- Text of the short form, as a result of the back-translation.

When using the short form to obtain consent, please note the following **required signatures:**

- The IRB – approved English informed consent form must be signed by:
  - The witness (fluent in both English and the language of the subject) (note that the interpreter may serve as the witness), and

- The person obtaining consent as authorized by the IRB (e.g., the investigator or research nurse).

- The short form must be signed by:

  - The subject (or by his/her LAR, if applicable), and

  - The witness (fluent in both English and the language of the subject) (note that the interpreter may serve as the witness).

A signed and dated copy of both the short form and the English informed consent form must be furnished to the subject.

A sample short form in English and in Spanish are available on the IRB website. Researchers wishing to use a short form are encouraged to use the appropriate translation of this sample short form.

2. Decision-Making Barriers

a. Adults with Impaired Decision-Making Capacity- the "Decisionally Impaired"

In Maryland, adults are defined as persons age 18 or older. A decisionally-impaired individual has a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive or emotional functions. Individuals who are decisionally impaired may suffer from many different conditions that could potentially affect their ability to reason and make sound choices. The level of impairment may fluctuate or progressively change over time. An individual's capacity may also be specific to the particular task, point-in-time, or decision-making circumstance. Examples of decisionally impaired individuals include those impaired by a stroke, traumatic brain injury, Alzheimer's disease, individuals under the influence of or dependent on drugs or alcohol, terminally ill patients, and individuals with mental illness such as schizophrenia, depression, or Post-Traumatic Stress Disorder. Other individuals who may be considered decisionally impaired with limited decision-making ability include individuals who have lost cognitive ability due to trauma, anesthetics, analgesics, or extreme pain, such as in an emergency room setting or preparatory to surgery.

The IRB will determine whether such subjects should be recruited or whether support mechanisms, such as consent granted by a LAR, are appropriate.

IRB considerations include:

- Can the prospective subject or his/her LAR understand the information?

- Can the prospective subject or his/her LAR retain enough of the information to think the question through?

- Is the prospective subject legally able to give consent?

- If not legally able to consent, should the prospective subject be involved in the discussion anyway?

- Are there alternatives to participation?

- Might the prospective subject feel any pressure to consent or refuse? If surrogate permission is necessary, might the LAR feel pressure to consent or refuse?

- Is the selection of subjects equitable?

The IRB will consider the following criteria before approving research involving adult participants with impaired decision-making capacity:

- The research is either minimal risk, more than minimal risk with a prospect of direct benefit, or more than minimal risk to the subject without a prospect of direct benefit, but of importance to the vulnerable population.

- That adequate provisions are made for obtaining consent from the subject or the subject's LAR.

- In some research, such as longitudinal studies involving progressive disorders or aging populations, enrolled subjects may be competent to consent on their own behalf at the outset, yet may experience effects of progressive or intermittent disorders that lead to decisional impairment during the course of the study. In these situations, IRBs and investigators should consider the need to discuss with the subjects whether they should designate someone to serve as a LAR at the outset of the study, consistent with all applicable laws. Even if a subject has consented on his or her own accord, a designated representative would be ready to step in as the LAR if the subject's ability to assess his or her own needs and interests becomes compromised during the study.

The protocol must describe when and how subjects will be assessed for decision-making capacity for formal consent and understanding of the proposed research. Competency should be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. Criteria for determining competence might vary according to the degree of risk or discomfort presented by the research procedures and the extent to which therapeutic gain can be anticipated.

Some approaches to this assessment include:

- A post-consent quiz documenting the participants' knowledge of critical elements in the informed consent document (i.e., nature of the illness being studied, voluntary nature of participation, ability to withdraw at any time, consequences of withdrawing, possible risks and benefits of participation, procedures involved, time required, confidentiality protections, and whom to call with any questions).

- The study investigators should ask a physician/psychologist outside the research team to evaluate the prospective subject's decisional capacity. The results of this evaluation conducted by a physician/psychologist not affiliated with the research study should be documented in the research file.

The IRB may consider additional safeguards to protect subjects, such as:

- requiring the involvement of subject advocates,
- requiring independent monitoring,
- requiring waiting periods,
- appointing a monitor to supervise the informed consent process.

Such decisions may be based on the amount of risk involved in the research and the likelihood that subjects will derive health benefits from their participation.

b. Legally Authorized Representatives (45 CFR 46.102(c); 21 CFR 50.3(l))

Federal regulations (45 CFR 46.102(c); 21 CFR 50.3(l)) define *legally authorized representative* (LAR) as "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 a subject is able to comprehend the facts of the research study and make a valid judgment, then the subject is the only one who may provide consent. Spouses and family members cannot grant consent if the subject is mentally capable to do so.

Federal regulations defer to state and local laws regarding who may serve as a "legally authorized representative" to consent to research. In Maryland, the principal law governing who may make health care decisions for another is the Maryland Health Care Decisions Act of 1993 ("HCDA") (Md. Code Health Gen. 5-605(a)(2)). The HCDA establishes who may make decisions regarding medical treatment for a patient (i.e., who may serve as a "surrogate") when the patient is **no longer able to make health care decisions personally and has not selected a health care agent.** The HCDA does not, however, address whether a surrogate may provide informed consent on behalf of a subject participating in clinical research. This was addressed through an advisory opinion by the Maryland Attorney General.

In short:

1. A surrogate (as established under the HCDA) has the authority to provide informed consent on behalf of a research subject if there is a reasonable potential for direct medical benefit to the subject;

2. A surrogate under the HCDA does not have the authority to provide informed consent for research involving treatment of mental disorders; and

3. No person, including a parent or another surrogate, can provide consent for a child or "other person under legal disability" to participate in nontherapeutic research or in studies in which there is more than minimal risk of injury or damage to the subject's health.

As stated above, Maryland law ***does not*** specify who may consent to research participation on behalf of an incompetent adult.

For the purpose of determining who may serve as a LAR of an incompetent adult, investigators should follow the Maryland law applicable to ”health care proxies”.

Under Maryland law, there are three kinds of health care proxies:

- a health care agent,
- a surrogate,
- a guardian.

Health Care Agent: A health care agent is someone appointed by an individual to make health care decisions. Usually, the health care agent steps in after the individual has lost the ability to make these decisions personally. Most health care agents are appointed through a written document called an advance directive. (Sometimes people call this a “durable power of attorney for health care”.) A health care agent also may be appointed by an oral, witnessed statement to a physician. This is just as valid as a written advance directive. A health care agent may be a family member or someone else. The agent has the authority to see that doctors and other health care professionals give the type of care the person would want. The agent should advocate for the patient. An advance directive appointing a health care agent is not the same as a living will. A living will allows a person to set out directions on medical treatment in advance. It is to be followed when the person has a terminal illness, is in a persistent vegetative state, or the end-stage of a serious illness, and can no longer speak for him or herself. A living will does not appoint an agent. However, a living will may be combined with appointment of an agent through an advance directive.

A **health care agent’s** authority depends on what the person’s advance directive says. A health care agent’s duties begin when the individual loses the ability to make health care decisions on his or her own (or, rarely, when the person wants to let the agent decide even though he or she still could). This is determined by a process outlined in the advance directive. If no process is identified, two physicians should certify that the person is incapable of making decisions concerning his or her own health care. (If the person is unconscious or unable to communicate, the certification of a second physician is not required.)

Surrogate Decision Maker: If no health care agent is available and the patient can no longer make health care decisions, Maryland law says which family member or friend can make health care decisions. This person (or sometimes more than one) is called a surrogate decision maker or surrogate for short. Unless the court already has named a guardian to make health care decisions (see below), the (1) patient’s spouse has the first right to be a surrogate and make these decisions on the person’s behalf. If there is no spouse – or the spouse is unavailable or unwilling to make decisions – an (2) adult child of the patient (or children, if more than one is available) can decide. If there is no adult child, then a (3) parent, followed by an (4) adult sister or brother can decide. If none of these relatives are available, a (5) friend or more distant relative may make decisions. In this case, the friend or relative needs to sign a statement about his or her regular contact with the patient and familiarity with the patient’s health and personal beliefs.

A **surrogate's** authority is the same as a health care agent except that a surrogate may not make a decision about sterilization or treatment for a mental disorder. Also, if a decision is against the use of life-sustaining procedures, the patient's doctor must certify that the patient is in one of three situations set out in the law – terminal condition, end-stage condition, or persistent vegetative state. If surrogates at the same level disagree, a patient care advisory or ethics committee at a hospital or nursing home can help resolve the situation.

Guardian of the Person: Sometimes a court names a guardian of the person, or guardian, for short, to make health care and other decisions for individuals. Guardianship might be necessary to get consent for a specific medical procedure, for ongoing medical care, or for placing a person in a safe living environment. Guardians usually need specific court approval to withhold or withdraw life-sustaining procedures.

A **guardian's** duties depend on the court's order and on Maryland law. A guardian often is responsible for making health care decisions and assuring that the person is living in a safe environment, but the court may limit this authority. A guardian may need to seek court approval for medical procedures that involve a substantial risk to the person's life, including a decision to withhold or withdraw life-sustaining procedures.

Please direct any questions regarding surrogates/legally authorized representatives to Adventist HealthCare General Counsel and IRB.

3. Illiterate English-speaking Subjects and Those Physically Unable to Sign the Informed Consent Form

The IRB allows individuals who speak and understand English, but do not read or write English, to enroll in a study by "making their mark" on the consent document, after going through the informed consent process. A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (2) is able to indicate approval or disapproval to study entry, they may be entered into the study. The consent form should document the method used for communicating with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party must witness the entire consent process and sign the consent document. While not required, a video tape recording of the consent interview is recommended.

III. RESEARCH SUBJECT'S BILL OF RIGHTS

As a part of the informed consent process, the IRB requires that all subjects enrolled in a research study receive a copy of the Adventist HealthCare Research Subject's Bill of Rights in addition to the IRB-approved informed consent form. The investigator (or approved representative) is responsible for ensuring this requirement is satisfied.

IV. MODIFYING THE CONSENT PROCESS

For research that is not regulated by the FDA (e.g., trials that do not involve investigational drugs or devices), the IRB may permit certain waivers of or alterations to the

informed consent requirements. The IRB may alter some of the elements of informed consent or waive them altogether, or the IRB may require all the elements of informed consent but waive the requirement that informed consent be written and signed by the subject.

A study which qualifies for waiver or alteration of the consent process may or may not qualify for a waiver of the HIPAA Privacy Rule's written authorization requirements as separate rules and regulations apply. See Chapter 9, "Medical Research and the HIPAA Privacy Rule," for additional information.

IRBs may not waive or alter the informed consent requirements for FDA-regulated research; however, provisions for research in an emergency setting and emergency use of a test article for research purposes exist. These provisions are explained in more detail in Chapter 8, "FDA-Regulated Research – Additional Issues."

A. Waiver/Alteration of Consent for Non-FDA Studies

An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above in Section II.A of this Chapter. The IRB also may waive the requirement for obtaining informed consent. For the IRB to alter or waive the elements of informed consent, the IRB must find and document that ***either*** of the following conditions exists:

- the research is to be conducted for the purpose of demonstrating or evaluating (i) federal, state, or local benefit or service programs that are not themselves research programs, (ii) procedures for obtaining benefits or services under these programs, or (iii) possible changes in or alternatives to these programs or procedures, and if the research could not be carried out practicably without the waiver; or

- 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 practicably be carried out without the waiver or alteration, and, whenever appropriate, the subjects will be provided with additional pertinent information after participation. (45 CFR 46.116(d)).

To approve a waiver or alteration of the informed consent process, the IRB must find and document that the above regulatory criteria are met and that the research is not subject to FDA regulations.

B. Waiver of Documentation of Consent

As allowed by OHRP regulations (45 CFR 46.117 (c)) and FDA regulations (21 CFR 56.109(c)), the IRB may waive the requirement to obtain written documentation of informed consent. A waiver of documentation of consent does not mean that requirements of the consent process are waived.

Even if a waiver of documentation is granted by the IRB, permitting the investigator to forego obtaining the subject's signature on a written consent document, the investigator still

must provide the subject with all of the information required to constitute a complete and appropriate informed consent process.

To approve a waiver of documentation, the IRB must find that the protocol-specific justification for waiving documentation satisfies regulatory criteria. Specifically, the IRB must determine that one of the following regulatory criteria for the waiver is met (note that (a) does not apply for FDA-regulated research):

a) Under OHRP (45 CFR 46.117(c)(1) the IRB must find and document either:

i. the only record linking the subjects 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 he/she wants documentation linking the subject with the research, and the subjects' wishes will govern; or

ii. 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;

or

b) For research subject to OHRP and FDA regulations, the IRB must find and document that the research involves no more than minimal risk to subjects and involves no procedures for which written consent is normally required outside of the research context. (45 CFR 46.117(c)(2), 21 CFR 56.109(c)(1)).

A separate set of rules applies to the HIPAA Privacy Rule's authorization requirement; a study which qualifies for waiver of documentation of consent may or may not qualify for a waiver of the Privacy Rule's written authorization requirements.

V. STUDIES INVOLVING SPECIAL CLASSES OF RESEARCH SUBJECTS: VULNERABLE SUBJECTS

Policies on informed consent for research with vulnerable populations are set forth in Chapter 6 of the IRB Handbook.

VI. DECEPTION OR WITHHOLDING INFORMATION (Not Applicable to FDA-Regulated Research)

A. Use of Deception in Research

There are times when investigators plan to withhold information about the real purpose of the study or purposely give subjects false information about some aspect of the research. As a result, the subject will not be able to give prospective fully informed consent. The use of deception or incomplete disclosure imposes special responsibilities on the investigator and the IRB. Minor deception, such as withholding specific points of interest in an attempt to prevent a bias in the results, can be acceptable, provided the subject is fully debriefed after participation. Risks stemming from major deception, such as leading a subject to believe that he or she has

committed a crime or has a disease, must be clearly counterbalanced by the benefits of the research as determined by the IRB.

Federal regulations prohibit the use of deceptive techniques that place subjects at "greater than minimal risk." If subjects are not placed at greater than minimal risk, the IRB may modify the normal informed consent process for research involving deception. Nevertheless, the waiver/alteration of the elements of consent must not adversely affect the rights and welfare of subjects, and must be essential to the ability to carry out the research. (45 CFR 46.116(d)).

Deception in research in most often found in behavioral and psychological research.

B. Justification and Debriefing

In order for the IRB to adequately review the research, investigators must justify and explain: (i) the necessity for deceiving subjects; (ii) how the potential benefits of the research justify the use of deception; and (iii) how the investigators will conduct the debriefing. In addition, investigators should include a debriefing script indicating the information subjects will receive regarding their participation in the research.

The IRB, in collaboration with the investigator, will determine whether subjects should be debriefed either after unwittingly participating in research or after knowingly participating in research that involved deception. In addition, the IRB may require that subjects, once debriefed, be asked whether their data may be used in the research. In most cases, it will be the investigator's responsibility to ensure that the subject leaves the research setting with an accurate understanding of the research and the necessity for the use of deception.

APPENDIX 1
SUBJECT COMPREHENSION TOOL

(Based on tool from University of California – Irvine)

Prospective Subject: _____ Date: _____

Protocol Title:

Protocol IRB #:

Record the prospective subjects' response to the following questions:

1. **Understanding:**
   What is the purpose of the research study? _____

_____

   What will happen to you in this research study? _____

_____

2. **Appreciation:**
   What are the potential risks of this research study? _____

_____

   What are the potential benefits of this research study? _____

_____

3. **Reasoning:**
   What alternative is there if you choose not to participate in this study? _____

_____

4. **Expressing a Choice to Participate:**
   Is your choice about whether or not to participate in this study a voluntary act on your part?

_____

For the research team:

Does the individual show sufficient comprehension of the research to give informed consent for this study?

☐ Yes ☐ No

_____

5. Printed Name of Evaluator Signature of Evaluator