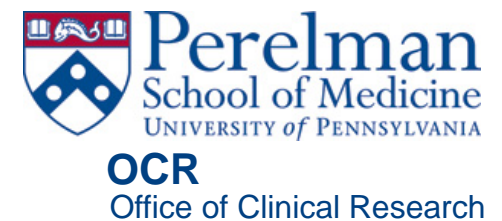


Flexibility and Informed Consent Process

April 30, 2014



Regulatory & Ethical Requirements for Informed Consent

Megan Kasimatis Singleton, JD, MBE, CIP

Associate Director, IRB

Dave Heagerty

IRB 8 Coordinator

Office of Regulatory Affairs - IRB



Overview

- ◆ **Ethical Principles & the Belmont Report**
- ◆ **Regulations**
 - Definitions
 - Requirements for the Consent Process
 - Required Elements of Consent
 - Optional Elements of Consent
- ◆ **When are waivers/alterations permissible?**
 - DHHS Regulations
 - FDA Regulations

Ethical Foundations for Informed Consent: The Belmont Report

◆ Belmont Report 1979

- Set forth three principles that serve as the foundation for ethical research with human subjects

◆ First Principle= Respect for Persons

- Recognize & Respect Individual Autonomy
- Protect those with diminished Autonomy
- “Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.”

Ethical Foundations for Informed Consent: The Belmont Report

- ◆ **According to the Belmont Report, consent contains three core elements:**
 - Information
 - Comprehension
 - Voluntariness

Information

- ◆ **Regulations outline specific elements that are considered to be necessary**
- ◆ **Beyond that, the Belmont Report suggests a standard of a “reasonable volunteer” should be applied**
 - The extent and nature of the information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

Comprehension

- ◆ The manner and context in which information is conveyed is as important as the information itself.
- ◆ Information must be adapted to the subject's capacity for comprehension.
- ◆ Investigators are responsible for ascertaining that the subject has comprehended the information. This obligation increases as the risk of participation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.
- ◆ Special provisions may be needed when comprehension is severely limited (age, cognitive impairment, etc). In these populations respect for persons occurs by acknowledging the wishes of these individuals and by the use of third parties to protect them from harm.

Voluntariness

- ◆ **An agreement to participate in research constitutes a valid consent only if voluntarily given.**
- ◆ **This element of informed consent requires conditions free of coercion and undue influence.**
 - Coercion: When an overt threat of harm is intentionally presented by one person to another in order to obtain compliance.
 - Undue influence: Occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance.
 - inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Regulatory Requirements for Informed Consent

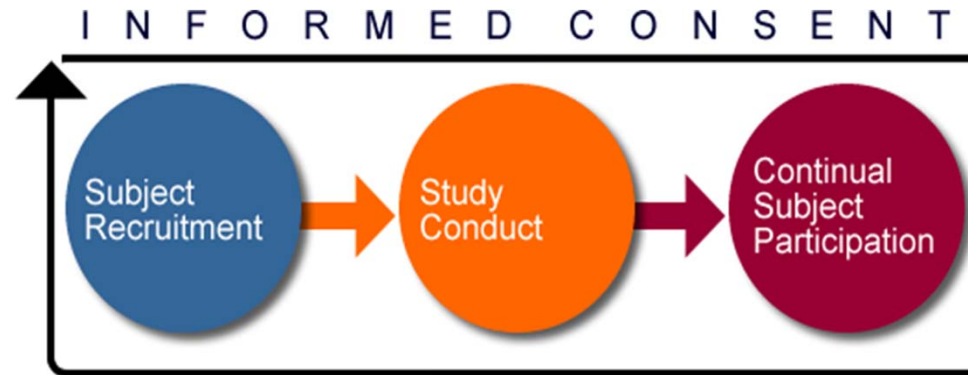
- ◆ **The regulations require that legally effective informed consent be obtained.**
- ◆ **Informed consent is legally effective if it is both obtained from the subject or the subject's legally authorized representative and documented in a manner that is consistent with the HHS protection of human subjects regulations and with applicable laws of the jurisdiction in which the research is conducted.**
- ◆ **The informed consent requirements in the DHHS/FDA regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed for consent to be legally effective**

Regulatory Requirements for Informed Consent

◆ 21 CFR 50.20 (FDA)-- 45 CFR 46.116 (HHS)

- The prospective subject must have sufficient opportunity to consider whether or not to participate
- The possibility of coercion or undue influence must be minimized
- The information that is given must be in language that is understandable to the subject.
- No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive legal rights or the researchers from liability.
- Consent must be documented

Informed Consent Process



- *Not* a form, but a **PROCESS**
- *Not* accomplished in a single session
- *Not* completed when the document is signed
- *Not* a release of liability
- *Not* meant to disclose information- but convey it
- **Must comply** with all regulatory requirements

Required Elements for Informed Consent

- ◆ **A statement that the study involves research**
- ◆ **An explanation of the purposes of the research**
- ◆ **The expected duration of the subject's participation**
- ◆ **A description of the procedures to be followed (experimental procedures must be identified)**
- ◆ **A description of any reasonably foreseeable risks or discomforts**
- ◆ **A description of any benefits to the subject or to others**

Required Elements for Informed Consent

- ◆ A disclosure of alternative procedures
- ◆ A description of how confidentiality will be maintained
- ◆ An explanation of any compensation/medical treatment available if injury occurs (required for greater than minimal risk research)
- ◆ Contact information for questions about the study, research subject's rights and who to call if injury occurs
- ◆ A statement that participation is voluntary
- ◆ A statement that the subject may refuse to participate/withdraw without penalty or loss of benefits

Optional Elements for Informed Consent

- ◆ **A statement that there may be unforeseeable risks**
- ◆ **The circumstances when subject participation may be terminated by the investigator**
- ◆ **Any additional costs to the subject**
- ◆ **The consequences of a subject's decision to withdraw/explanation of how to withdraw**
- ◆ **A statement that significant new findings which may affect willingness to continue participation will be provided to the subject**
- ◆ **The approximate number of subjects involved in the study.**

When are waivers/alterations permitted?

- ◆ **Waiver of consent (DHHS regulations)**
- ◆ **Waiver of documentation of consent (DHHS regulations)**
- ◆ **Other Alterations of consent (e.g. Deception)**
- ◆ **Exception from Informed Consent (FDA regulations)**

Criteria for a Waiver of Consent

- ◆ **ALL of these requirements must be met:**

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

Criteria for Waiver of Documentation of Consent

- ◆ **ONE of the following situations must apply:**

- 1. 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
- 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.

Alteration of Consent

- ◆ **On occasion providing full information up front may impair the validity of the research**
- ◆ **In all cases of research involving incomplete disclosure (e.g. deception) the following must be true:**
 - (1) incomplete disclosure is truly necessary to accomplish the goals of the research,
 - (2) there are no undisclosed risks to subjects that are more than minimal, and
 - (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them.
- ◆ **Important caveats:**
 - Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects.
 - Truthful answers should always be given to direct questions about the research.
 - Cases where disclosure would destroy/invalidate the research must be distinguished from cases where disclosure may simply affect participation.

Are waivers of consent permitted under the FDA regulations?

- ◆ **Generally waivers of consent are not permitted when the research involves an FDA regulated product**
- ◆ **The FDA does not recognize waivers of documentation of consent**
- ◆ **FDA does permit an exception under 21 CFR 50.23 if the following criteria are met (emergency setting)**
 - The human subject is confronted by a life-threatening situation necessitating the use of the test article.
 - Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.
 - Time is not sufficient to obtain consent from the subject's legal representative.
 - There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

Are waivers of consent permitted under the FDA regulations?

- ◆ **FDA also allows emergency research to be performed without prospective informed consent under an exception called “Exception from Informed Consent” (EFIC)**
- ◆ **Many additional regulatory requirements for these types of studies**
- ◆ **See:**
<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm249673.pdf>

Application of the Principles and Regulations

Laura Fluharty, MPH
Operations Manager
Office of Clinical Research



Example 1: Mixed Model Consenting Approach with Waiver of Documentation

Example of a Study with a Mixed Consenting Approach

- ◆ You receive a Phase III, randomized, double blinded, placebo controlled study in which there is a laundry list of inclusion and exclusion criteria
- ◆ Some of the criteria are lab related but many are potentially self reported items such as
 - Alcohol use
 - Tobacco use
 - Sexual partner availability
 - Thoughts of depression
 - Limited physical ability
 - Limited feeling of vitality

Study with a Mixed Consenting Approach

- ◆ **Based on the extensive inclusion and exclusion criteria it is anticipated that it will take screening roughly 70 men in order to enroll one in to the trial**
- ◆ **The overall enrollment goal for the trial is 1,000 and your site is expected to enroll 70 men**
- ◆ **Funding is contingent upon reaching certain enrollment milestones in the trial**

Mixed Consenting Approach

- ◆ **This means in order to reach your enrollment goal you will need to go through the full informed consent form process with 70 men to enroll 1**
- ◆ **The consent process is not merely signing the consent form but going through the whole 25 page document with the participant and making sure they understand everything that is being asked of them**
- ◆ **You will be going through that process 4,900 times and most of the procedures and details in the consent will not apply to the majority of the men**

Mixed Consenting Approach

- ◆ **This is a high risk study and subjects who are being randomized need to be fully informed**
- ◆ **Many of the screening procedures also involve labs and invasive procedures for which informed consent is required, necessary and appropriate**
- ◆ **But there are some questions which could be asked over the phone prior to weed out the number of subjects that need to be brought into the clinic**

What Can You Do????

Using Multiple Consent Forms

- ◆ **Design a graduated consent process to slowly weed people out:**
 - Screening Visit 1- over the phone
 - Screening Visit 2- in clinic to further assess eligibility and plan enrollment visit
- ◆ **Would Screening Visit 1 meet the criteria for a waiver of documentation of consent?**

Waiver of Documentation of Informed Consent

- ◆ **One of the following two criteria must be met:**

- The research informed consent document would be the only document linking the participant to the research study and the primary risk of the study is loss of confidentiality

– OR

- The research involves no more than minimal risk and involves procedures for which consent is not typically warranted
 - Although the overall study itself is greater than minimal risk the questions that are being asked over the phone are minimal risk. If we think about these procedures independently, anonymous questions over the phone meet the definition of minimal risk and are something for which consent is not usually obtained.
- In this case option #2 would fit

Graduated Consent Approach

- ◆ **To conduct this approach look to the protocol to determine which questions can be asked over the phone**
- ◆ **Want to avoid any invasive or overly personal questions over the phone as this may turn people off and their answers are less likely to be truthful**
 - For example: questions about illegal drug use or sexually transmitted diseases

Screening Visit 1

- ◆ **Will involve interested potential subjects calling into the clinic and being asked a series of screening questions over the phone.**
- ◆ **Before any questions are asked of the potential participant their consent is obtained over the phone.**
- ◆ **The consent involves a brief description of the study and explains the questions that are going to be asked. Script for screening over the phone will need to be approved by IRB as will the waiver.**
- ◆ **Documentation of affirmative or negative consent will be recorded on the participant's case report form and recorded.**

Example #2: Waiver of Documentation of Consent

Protocol Description

- ◆ You receive a protocol in which you will be going into predominately homosexual nightclubs to interview men who have sex with men (MSM) about their sexual behaviors, contraception use and STD status
- ◆ You are looking for public health patterns and conducting a needs assessment in the study
- ◆ The data will be anonymous but you will be interviewing people in person

Consent Alteration

- ◆ **There is no doubt that you need to inform participants that you are collecting very sensitive information about them and that it will be used in a research context.**
- ◆ **It is very important to let people know how the sensitive and personal information they are providing is being used.**
- ◆ **However all of the study data is de-identified and the only document linking the participant to their answers would be the signed consent.**

Waiver of Documentation of Informed Consent Is Applicable If.....

- ◆ **One of the following two criteria must be met:**

- The research informed consent document would be the only document linking the participant to the research study and the primary risk of the study is loss of confidentiality
 - Or
- The research involves no more than minimal risk and involves procedures for which consent is not typically warranted
- In this case the first option above would fit

Waiver of Documentation of Informed Consent

- ◆ It would be riskier, in the case of this study, to get the signature of men participating
- ◆ However, just because the signature has been waived, you still need to go through the consent process with the participant
- ◆ Develop a consent form which describes all of the details of the research trial and includes all required elements of consent- this along with the waiver will need to be approved by the IRB
- ◆ Discuss risks with the participant and ask them if they would like to have their consent documented- their wishes dictate the documentation
- ◆ Document review process with each participant enrolled and interviewed in study on case report form

Example #3: Waiver or Alteration of Consent

Retrospective Chart Review

- ◆ You receive a protocol which involves a retrospective chart review of 785 charts from 1996-2012
- ◆ All of the data will come from charts and will not involve contacting patients for follow up
- ◆ Identifiable information will not be recorded from the charts

Would an Alteration or Waiver of Consent Apply?

- ◆ **The study is no more than minimal risk**

- The study does not record any identifiable information about participants and therefore poses no more than minimal risk
- Study could not practicably be carried out otherwise
 - There are far too many charts and some of the contact information may be very outdated
- The waiver or alteration will not impact the rights or safety of the subjects
 - Although researchers are looking at medical charts no identifiable information will be recorded
- Whenever applicable additional information will be provided to the participant.
 - There would be no need to contact participants with additional information in this case

Example #4: Waiver of Documentation of Consent with an Opt-Out Approach

Protocol Description

- ◆ You receive a protocol in which 2 different clinics are being randomized to two different length dialysis procedures.
- ◆ The care of participants in the clinics is still being managed by their doctors but their dialysis time may be extended, if it is considered clinically fit, if they are in one clinic versus the other.
- ◆ Information on patient outcomes will be collected but no identifiable information will be collected.
- ◆ Data on patient outcomes is typically stored in the providers' databases but in this case will also be stored in the trial DCC database.

Consent Issues

- ◆ **This research is being conducted in the provider clinics and there is no one there who is trained and able to go through the consent process with people in the clinic.**
- ◆ **There is no additional data being collected outside of what is normally collected and stored in the dialysis providers' databases but the data is also being sent to a DCC for analysis**
- ◆ **But if someone is in the clinic that is randomized to the longer procedure time frame they may have extended dialysis**

What is a Viable Consent Option

- ◆ **There is no one in clinic who is qualified to go through the consent process with the participant because they are not prepared to answer questions about the study.**
- ◆ **There is no data being collected which would not normally be collected.**
- ◆ **But participants are part of a trial and should be informed of this and data is being sent to a DCC.**
- ◆ **Possible Solution- A shortened consent form which contains only the basic required elements and does not require a signature. However gives the option of opting- out by calling a specific number.**

Would a Waiver of Documentation Apply?

- ◆ **The consent document would be the only record linking the participant to the study and the principal risk would be loss of confidentiality.**
 - The consent document would be the only document linking the participant to the trial since no identifiable information is collected.
- ◆ **The study is no more than minimal risk and involves no procedures for which outside consent is typically required**
 - While the dialysis procedures participant are undergoing may be risky, the study itself extends time of dialysis by a few hours and will not take place if the physician feels it is not clinically warranted
- ◆ **Both options one and two would apply**

Conclusions

- ◆ **Look for creative solutions based on the inclusion and exclusion criteria in the protocol.**
- ◆ **Be familiar with the different consenting options available**
- ◆ **Do not be afraid to try and make the case for an alteration to the consent process if you think it is warranted- the worst that can happen is it will not be approved.**
- ◆ **Reach out to the IRB, or OCR, for advice with the process.**
- ◆ **Just because a study may have a waiver of documentation or alteration of consent does not mean you can skip going through the process of explaining the study to the participant. Their comprehension should be the number one priority.**

