Disclaimer

- Nothing in this presentation constitutes the provision of legal advice.
- You should obtain legal advice from your lawyer or a lawyer who has been formally retained by your organization
- Possession of this presentation by you in hard or soft copy does not establish an attorney-client relationship between you or your organization and me or my firm.

Overview

- Required elements of the informed consent form (the “ICF”)
- Recent OHRP determination letters
- OHRP ANPRN
- Therapeutic misconception and its effect on informed consent
- Consent discussions by non-licensed individuals
Where Are the Regulations?

- 21 CFR § 50.25 and 45 CFR § 116
- Almost identical; FDA has some added requirements
- Almost all SWOG studies will be governed by both sets of regs

Required Elements

- Statement that the study involves research
- Explanation of the purposes of the research
- Expected duration of the subject’s participation
- Description of the procedures to be followed
  - Including identification of procedures which are experimental

Required Elements

- Description of any reasonably foreseeable risks or discomforts to the subject
- Description of any benefits to the subject or others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
Required Elements

- Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
  - Include that the FDA may inspect the records

- For research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatments are available if injury occurs
  - and, if so, what they consist of, or where further information may be obtained

Required Elements

- Explanation of whom to contact for answers to pertinent questions about the research and subject’s rights

- Statement of whom to contact in the event of a research related injury to the subject

- Statement that participation is voluntary

Required Elements

- Statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled

- Statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled
Additional Elements

- When appropriate, must also include:
  - Statement that particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
  - Statement of anticipated circumstances under which subject's participation may be terminated by the PI without regard to the subject's consent
  - Any additional cost to the subject that may result from participation in the research

More Additional Elements

- When appropriate, must also include:
  - Consequences of the subject's decision to withdraw and procedures for orderly termination of participation by the subject
  - Statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue will be provided to the subject
  - The approximate number of subjects involved in the study

New FDA Requirement

- For applicable clinical trials, as defined in 42 USC § 282(j)(1)(A):
  - "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."
Exculpatory Language

- FDA Guidance: "The examples below would be in violation of 45 CFR 46.116 and 21 CFR 50.20 because in each example, the waiver or release has the general effect of freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault, or guilt."
  - I waive any possibility of compensation, including any right to sue, for injuries that I may receive as a result of participation in this research.
  - If you suffer a research-related injury, neither the institution nor the investigator can assume financial responsibility or liability for the expenses of treatment for such injury.
  - In the event that you suffer a research-related injury, your medical expenses will be your responsibility or that of your third-party payer.

OHRP on Exculpatory Language

  - From 1996
  - Examples of Exculpatory Language:
    - By agreeing to this use, you should understand that you will give up all claim to personal benefit from commercial or other use of these substances.
    - I voluntarily and freely donate any and all blood, urine, and tissue samples to the U.S. Government and hereby relinquish all right, title, and interest to said items.
    - By consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.
    - I waive any possibility of compensation for injuries that I may receive as a result of participation in this research.
Draft OHRP Guidance

  - From August 2011

Noncompliance

- Widespread and frequent
- List of recent determinations on OHRP website
  - Section F
    - 8 categories of non-compliance regarding consent

Recent OHRP Determination Letters Regarding Informed Consent

- Determination Letters found at:
- Two of last four are regarding consent
- Client cited for failure to have all required elements in ICF
  - Used templates from cooperative group approved by NCI
  - OHRP: “The institution is responsible for compliance with federal regulations.”
Recent Determination Letter

• "We have determined that many of the informed consent documents provided in your response do not appear to include all the pertinent alternatives to participation in the research . . ."

• "Your response stated that some of the studies were conducted under an FDA IND, and it would be inappropriate to offer this experimental therapy outside of the study and that the consent forms for some of these studies did not include the investigational intervention as it is not part of standard of care."

More from Recent Letter

• "HHS regulatory requirements at 45 CFR 46.116(a)(4) do not specify that only information about standard of care interventions must be provided to subjects, but must include a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject." [emphasis in original]

• "Your response also stated that offering as an option the use of some over the counter interventions could be viewed as encouraging self-medication without medical supervision . . . We note that the forms could have advised subjects to obtain such treatments only under medical supervision, if indeed, for the particular treatment in question, such supervision would be appropriate."

Regarding Requirement That Subjects Agree to Future Research

• "We determine that the consent form provided for a study indicate [sic] that subjects may be coerced into participating in open-ended, future research involving their biospecimens, in contravention of the regulatory requirements at 45 CFR 46.116."

• "Your response notes that standard of care therapy was not withheld from potential subjects if they did not participate; there were no urgent timelines placed upon potential subjects in which to make a decision; and agreeing to participate in the biobanking portion of the study did not expose the potential subject to any greater risk than the nonbiobanking portion of the study since no genetic testing is planned."
Regarding Requirement That Subjects Agree to Future Research

• “However, we note that the study did hold out the prospect of direct benefit to the subjects which may be difficult for them to obtain without their agreement to participate in the biobanking portion of the study. Thus, they are being denied the right they have to participate in the study “alone,” without participating in the unrelated open-ended future biospecimen research. The level of risks presented by biospecimen research is not relevant to this issue. Even if such research is very low risk, subjects, just because they are enrolling in a particular clinical trial, do not generally give up their autonomy regarding deciding whether their identifiable biospecimens can be used for wholly open-ended and unspecified future research.” [emphasis added]

Take-Aways

1. Create and use a checklist!
2. Use it even when presented with a template ICF from a reputable source
3. Do not have exculpatory language or language that requires subjects to give up their rights in the ICF
4. Do not condition participation in the trial upon agreement to participate in future unrelated research

Jesse Gelsinger

• Rare metabolic disorder
  – Ornithine transcarbamylase deficiency syndrome (“OTC”)
• June 22, 1999 entered a gene therapy clinical trial after a 45-minute consent discussion with the PI (that included his parents)
• Gene infusion Sept 13
• Suffered irreparable brain damage and vital organs started to shut down
• Taken off life-support Sept 16
• Father ultimately learned that efficacy never shown in humans prior to trial
Jesse Gelsinger

- Although Gelsinger and his family were under the impression that the pre-clinical animal studies had affirmed the trial’s safety, two monkeys had actually died. This information appeared on the consent form submitted to the NIH review board, but did not appear on the form signed by Jesse.
- The Penn researchers did not disclose to either the Gelsingers or federal regulators that human volunteers in the same study had suffered adverse reactions - side effects serious enough to have halted the trials had they been reported.
- The lead researcher in the Penn study - James Wilson - did not disclose to the Gelsingers that he was conducting the clinical trial with a private company in which he had a stake. Wilson had a direct financial interest - not merely an academic one - in the trial’s successful outcome.

Ten Years Later: Jesse Gelsinger's Death and Human Subjects Protection by Osagie K. Obasogie, Bioethics Forum October 22nd, 2009  

The OHRP ANPRM

- 76 Fed Reg 44512 (July 26, 2011)  
  - Or www.hhs.gov/ohrp
- Considering number of modifications to regs to "improve" consent forms:
  - Prescribing content that must be in ICF with greater specificity than in current regs
  - Restricting inappropriate content
  - Limiting acceptable length
  - Prescribing how info should be presented
  - Reducing institutional boilerplate
  - Making standardized ICFs available
- 6 questions posed

OHRP ANPRM

- Also looking at possibility of revising regs regarding:
  - Waiver of informed consent or documentation of consent in primary data collection
  - Strengthening consent protections related to reuse or additional analysis of existing data or biospecimens
  - Looking at possibility of allowing single, general authorization to cover range of future unspecified research
- Watch for NPRM!
Therapeutic Misconception

- What is it?
  - Subject believes clinical trial was designed to treat his/her illness or disease

- How does it affect “informed” consent
  - Subject not making an informed decision

- PI and research personnel can also have it!
  - “This is cutting edge medicine”
  - “This is the best treatment available”
  - “Inflicts” the consenting process

Some Examples

- Amgen halted a Phase III trial of ganitumab for pancreatic cancer after an outside monitoring panel concluded that the drug was unlikely to improve the survival of patients with an advanced form of the disease. (NYT, 8/10/2012)

- FDA revoked its approval of the drug Avastin as a treatment for breast cancer. Clinical trials had shown that the drug was not helping breast cancer patients to live longer or to meaningfully control their tumors, but did expose them to potentially serious side effects like severe high blood pressure and hemorrhaging. (NYT, 11/18/2011)

One More

- ABMT with HDC for advanced breast cancer
  - False Hope: Bone Marrow Transplantation for Breast Cancer

- Clinical trial is suggested treatment by NCCN for some patients depending on their cancer and stage
  - Does not mean that we know the investigational treatment will help
    - Might even hurt
Consent Discussions

- 45 CFR 46.116
  - "Except as provided elsewhere in [the regulations], no investigator may involve a human being as a subject in research covered by [the regulations] unless the investigator has obtained legally effective informed consent . . . ." (emphasis added)

- OHRP FAQ on consent:
  - "For the purposes of the HHS regulations at 45 CFR part 46, "investigators" are individuals who conduct human subjects research projects, including individuals directly involved in seeking the voluntary informed consent of potential subjects. Investigators can include physicians, scientists, nurses, administrative staff, teachers, and students, among others."

Consent Discussions by Unlicensed Personnel

- Often happens outside clinical trials

- Is obtaining consent the practice of medicine or nursing?
  - Are there State requirements?

Questions??