Clinical Investigator Training Course

Informed Consent and Ethical Considerations

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Informed Consent

An ethical imperative with 100 shades of gray

Meaning –there is right and wrong and then there is opinion of what is right and wrong

Currency of the Challenge

- FDA issued draft guidance in July 2014 and gave 60 days for the comment period.
- 353 comments came flooding into the FDA
- 23 comments were posted citing concerns that the ICF document will be too complicated among other things

Informed consent can never truly be informed because the research is not well designed, well conducted and free from problematic bias and honest reporting

Informed Consent

Is a **process** of information exchange beginning with recruitment that may include, in addition to reading and signing the consent document, subject recruitment materials, verbal instructions, question/answer sessions and measures of subject understanding.

Consent Document

The basis for a meaningful exchange between the investigator and the subject.

NOTE: The document is NOT INFORMED

Shared Responsibility

Institutional Review Boards (IRBs), clinical investigators, and research sponsors all share responsibility for ensuring that the informed consent process is adequate

Background

- The Human Subject Protections regulations have now been in place for more than 30 years and yet “Informed” consent issues still rank among FDA’s top findings in FDA audits.
- So why?

IT’s complicated

Current Regulations

- Generally, not much has changed in the Informed Consent Regulations since they were codified.
- 21 CFR 50 was originally codified in May 1980 and last updated in 2013.
- 45 CFR 46 (Protection of Human Subjects) was originally codified in 1991) and last updated in 2009

Let Us Begin

Where the Regulations Lie

- HHS – if supported by federal funding – 45 CFR 46.
- FDA – 21 CFR Part 50 – all drugs and devices

Differences

- FDA, but not HHS, provides for an exception from the informed consent requirements in emergency situations.

FDA vs. HHS

- HHS provides for waiving or altering elements of informed consent under certain conditions. FDA has no such provision because the types of studies which would qualify for such waivers are either not regulated by FDA or are covered by the emergency treatment provisions (§ 50.23)
- FDA explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's medical records when they pertain to the study.

21 CFR 50 .25(d)

- The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclose for informed consent to be legally effective.

General Requirements (50.20)

1

Obtain **legally effective** informed consent from the subject or legally authorized representative

This means that the State has some say

Age of Consent

- While California sets its minimum age of consent at 15, Stanford sets it at 18
- Stanford IRB requires that anyone between the ages of 7-17 should give assent.

Assent

- Assent is more complicated - Regulations 21CFR 50.55 discuss assent of children and generally leave the issue up to the IRB. The IRB must take into account the ages, maturity and psychological state of the children involved
  - Stanford IRB has a standard language template for assent documents

Updates -Legally Authorized Representative

- FDA
  - In April of 2014 FDA released a guidance : The Meaning of “Spouse and “Family” .....
  - FDA interprets “spouse” or “family” to include individuals of the same sex who are lawfully married and whose marriage is valid in the state, territory or foreign nations where it took place. These terms also include same-sex spouses whose marriages are valid in the state, territory ,or foreign nation where they live
  - Stanford follows the California Code which is consistent with Federal Code (Section 24178)

Federal/State/IRB

- Confusing, but generally speaking..
  - Federal Law is the minimum standard.
  - States can require more strict regulation
  - IRB can require even more strict beyond the state but the IRB cannot make requirements that are less stringent than the State and thus the Federal Government.

And this is WHY is gets messy

General Requirements (50.20)

2

There must be no coercion or undue influence

General Requirements (50.20)

3

Information must be in a language that is understandable to the subject.

NOTE: The regulation does NOT say it must be at a 8th grade reading level. No regulation actually says that

Accepted Guidelines

- FDA, OHRP, NCI, NIH
  - Consent forms should be written as a 6th – 8th grade reading level.
  - Essentially – Consent document should be understandable to the patient population at the local facility. Documents should be written at an eighth grade reading level of lower

Stanford IRB

- "According to federal guidelines, consent form language should be suitable for the general public, written at the 8th grade level"
  - This is their local policy
- Stanford has a handy "lay language guide" on their website

Important Distinction

There is literacy and there is health literacy

Health Literacy and Informed Consent

- More than one third of U.S. adults (77 million people) have below basic health literacy
- Only 12% of Adults have proficient health literacy
- One-half of U.S. adults have basic or below basic quantitative literacy and are challenged by numerical presentations of health, risk, and benefit data

Health Literacy

- Calculating cholesterol levels and blood sugar levels, measuring medications and understanding nutrition labels.
- Misinformation about the body as well as the nature and causes of disease.
- Understanding of the relationship between lifestyle factors such as diet and exercise

Health Literacy

- Can affect compliance with investigational product regimens
- Compliance with visits

Boils Down To -

- Keep consent language simple –both written and spoken
- Evaluate understanding before, during, and after introduction to information
- Be mindful of cultural differences
- Check for understanding

General Requirements (50.20)

4

No exculpatory language through which the subject or the representative is made to waive or appear to waive right or release

Elements of Informed Consent

8 ABSOLUTE ELEMENTS

- Description of the investigation
- Risks and discomforts (reasonably foreseeable)
- Benefits that may be reasonably expected
- Alternative procedures or treatments
- Confidentiality
- Compensation and medical treatment in the event of injury
- Who to contact for answers to questions
- Statement that participation is voluntary

Additional Elements When Appropriate

- Unforeseeable risks
- Involuntary termination of subjects Participation
- Additional costs to subject
- Consequences of the decision to withdraw
- Providing significant new findings
- Number of subjects

Documentation of Informed Consent

- ...Informed consent shall be documented by the use of a written informed consent form that is approved by the IRB and signed and dated by the subject or the subjects legally authorized representative at the time of consent. A copy shall be given to the person signing the form. (21 CFR 50.27)
- Note to self. The HHS 45 CFR 46 only requires a signature but not the date. (45 CFR 46.117(a))
- Stanford IRB - signature and Date of subject and person obtaining informed consent-**end of story**

Updates to 21 CFR 50

Elements – 2011 -state that trial is to be listed on www.ClinicalTrials.Gov when applicable. Ok so when is that

- Basically anything but a phase 1 trial

Updates – 21 CFR 50

- 2013 – 12 years in the making, FDA finalized the 21 CFR 50 and 56 (IRB Regulations) to provide for additional safeguards for children enrolled in FDA-regulated research
- IRB takes a special role in assuring that children are protected
- Stanford has provisions in place to assure proper permissions from parents. Guardians and assent of children

Does FDA Approve Consent Documents?

- For IND trials there is no specific requirement to submit consent form with application.
- For IDE trials – sponsor must include copies of consent as well as all informational materials to FDA for approval. They review based on adherence to Federal Regulation.

Full Stop as they say

Now Back to Our Show

Stanford

- ***The principal investigator is responsible*** for ensuring that each research participant voluntarily gives informed consent before that individual participates in any research activities. The protocol director/principal investigator is ultimately responsible, even when delegating the task of obtaining informed consent to individuals who are trained and knowledgeable about the research

Consent Process

- Subjects must be consented before any trial procedures are performed.
  - Some have checks for this by entering the time consent was obtained in the source documents
- Site personnel must ensure that the subject has signed or initialed all areas of the consent that require signatures or initials

Consent Process

- Provide subject with adequate information
- Allow subject time to absorb the information
- Facilitate comprehension of the often complex information
- Allow time for dialogue
- Reinforce that participation is voluntary

Delegation of Consent Interview

- FDA – The Investigator can delegate this responsibility as long as the person wo who it is being delegated is qualified by education, training, and experience
- NOTE: The Investigator is still responsible for the conduct of the clinical trial

Delegation

Individuals with the correct experience and judgment complete an “informed” consent discussion and open dialogue with the potential study subject to discuss all possible adverse events, eligibility criteria, contraindicated medical histories, and results of participation, thus further pre- venting the inappropriate enrollment of an ineligible study subject.

Delegation of Consent Interview

How does this play out at Stanford?

- The Consent template includes a signature and date line for the subjects and the PERSON OBTAINING CONSENT

Delegation

It is highly important that persons who are delegated the responsibility to obtain informed consent are on the Delegation of Authority Log. They also should be listed on this log before they ever do anything associated with the trial

The Principle Investigator

- Does the Investigator have to sign the informed consent?
- NO – The signing and dating by the person conducting the informed consent discussion is part of the ICH-Guidelines but not FDA regulations

Electronic Signatures?

- The HHS and FDA allow electronic signatures on consent documents as long as they adhere to the applicable regulations (21 CFR 11)
- While allowed, Stanford has no mechanism to use these are the moment. There fore you must obtain wet signatures for all consent documents

Process

- If you have a process where the Investigator/ sub-Investigator performs the discussion with the subject and the study coordinator or designee obtains the signatures, you should have this process clearly documented such that auditors understand it.

Process and Re-Consent

- What happens when you have protocol amendment that affects the Consent Document?
  - Subject must re-consent at next visit. Not the end of the study
- What if they do not want to re-sign?
  - Subject must be exited from the study

Stanford Informed Consent

- Research compliance.Stanford.edu
  - One stop shopping regarding regulations, guidance, templates, state law
  - ICF template includes all necessary information with instructions
    - Elements of consent
    - Patent Bill of Rights
    - HIPAA language (where necessary)

What Are The Consequences For Consent Issues?

- Patient data may not be included in the study – NOTE: This actually happens. If we don't have the consent of the subject, we technically cannot include the data in the report to the FDA. Many sites simply say "whoops"
- Site may not get paid for the patient/s
- Site and the sponsor may receive an FDA 483 or Warning letter

Warning Letters Of Note – Columbia University Medical Center

- Dr. Lobo as the Sponsor
  - You failed to ensure proper monitoring including:
    - Failure to identify that the Investigator did not obtain informed Consent for 28 out of 50 subjects
    - Failure to identify that the IRB approval had lapsed from March 31 to June 3
    - Four subjects were not dosed according to the protocol

Warning Letters Of Note – Columbia University Medical Center

- Dr. Zimmerman as Investigator
  - You failed to obtain informed consent for 28 our of 50 subjects
  - Four subjects were not dosed according to the protocol

Let’s not forget HIPAA

HIPAA Authorization and Informed Consent

- These are not the same thing
- If HIPAA language is incorporated into an informed consent then the IRB can review it for completeness.
- If you have a stand alone HIPAA authorization you do not need IRB approval. The document just has to adhere strictly to the law.

What About the HIPAA Authorization?

- NOTE: HIPAA compliance is the responsibility of the site and cannot be transferred to the sponsor. As such, the sponsor cannot dictate how you comply with HIPAA.
- Sponsor cannot have PHI without valid HIPAA authorization
- If you are a covered entity and you collect patient information without Authorization you will get fined and you will have to retract all the data

Research Use and Disclosure of PHI With Individual Authorization

- Patient authorization elements:
  - The information,
  - Who may use or disclose the information
  - Who may receive the information
  - Purpose of the use or disclosure
  - Expiration date or event
  - Individual's signature and date
  - Right to revoke authorization
  - Right to refuse to sign authorization
  - A statement about the potential for the PHI to be re-disclosed by the recipient

Revocation of Authorization

- A subject has the right, at any time to revoke their HIPAA authorization.
- Must be done in writing
- The data you have already collected can stay in the database but you cannot collect any new data except if the subject has an adverse event that needs to be tracked. The government allows for the collection of this information for safety reasons.

California Extras

California Cancer Clinical Trials Law

- The law specifically covers cancer patients who participate in a Phase I, II, III, or IV clinical trial for cancer treatment.
- It is important for you to tell your patients who are enrolled in, or considering enrolling in, a clinical trial about the law because it affords them the financial freedom to participate in a study and benefit from innovative therapies and protocols, with far fewer worries about how to pay for the care.
- Trial must be pre-approved by FDA, NIH, DOD, VA

California Clinical Trial Mandates

- California, for example, requires clinical investigators to provide subjects with a signed and dated copy of the "**California Experimental Subjects Bill of Rights**" in addition to the study consent form. Violations of the California law are considered a misdemeanor and are subject to one year in jail and a $10,000 fine
- Under California law, all study protocols and consent forms involving Schedule I and Schedule II controlled substances must be reviewed and approved by the California Research Advisory Panel prior to study start—this is in addition to federally required IRB review and approval. Violations of the California law also are considered criminal offenses and are subject to fines and imprisonment.

Challenges To Informed Consent

- We never have complete control over the information that is presented to a prospective subject
- Information comes in a context and is delivered with a set of biases
- Information-even if reliable-may distract or mislead rather that help a decision
- It is hard to make complex information intelligible to a diverse audience

In Summary

The Effective Investigator needs to ensure that there are adequate mechanisms in place to ensure that the legally effective consent is obtained for every subject