Transforming Ethical Review...

Compliance Issues Involving E-Consent in Research

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Technology is Everywhere!
Discussion Topics

- Informed Consent Refresher
- Benefits of Electronic Consent
- Unique Issues to Consider in E-Consent
- Current and Developing Models
- IRB Considerations
The Belmont Report

- Respect for Persons
  - Information
  - Comprehension
  - Voluntariness
- Beneficence
- Justice

Informed Consent Regulation/Guidance

- Department of Health and Human Services: 45 CFR 46 (1974)
- ICH E6 Good Clinical Practice: Consolidated Guidance
Informed Consent - Generally

- Must be legally effective
- Must provide sufficient opportunity to consider whether or not to participate
- Must minimize the possibility of coercion or undue influence
- Must be understandable
- Must not appear to waive any of the subject’s rights or release the investigator, the sponsor or the institution or its agents from liability or negligence
- See 45 CFR 46.116(a)

Informed Consent – Required Elements

- Study involves research
- Purpose of the research
- Expected duration of participation
- Procedures to be followed
- Identification of experimental procedures (if applicable)
- Foreseeable risks
- Benefits
- Alternatives
- Confidentiality (FDA may inspect)
- Compensation for injury / treatment for injury (if greater than minimal risk)
- Who to contact for injuries, questions about rights, questions about study
- Participation is voluntary
  - Refusal does not involve penalty or loss of benefits
  - Subject may discontinue at any time
- ClinicalTrials.gov (if applicable)
Informed Consent – Additional Optional Elements

- Unforeseeable risks to subject
- Circumstances that may result in participation being terminated without subject’s consent
- Additional costs resulting from the research
- Consequences of subject’s decision to withdraw and early termination procedures
- Procedures for orderly termination of participation by subject
- If there are new findings that might affect the subject’s willingness to continue in study – subject will be told
- Approximate number of subjects
- Amount and timing of subject payments

Consent Documentation

- Document is accurate and complete.
- Subject (or legally authorized representative) must sign and date consent form and receive a copy.
- Site to document that consent was obtained prior to subject participation.
- ICH GCP E-6 requires signature of person conducting consent process.
- For clinical research, if the subject cannot read, an impartial witness will witness the consent process and sign and date the form.
- For non-readers, FDA does not require a witness signature, but if a site chooses to add a witness signature, the witness must sign and date.
- Assent of individuals who cannot consent due to age or diminished capacity must be considered and documented where appropriate.
HIPAA Privacy Rule Authorization

- Generally, a covered entity must have an authorization to use or share protected health information (PHI) for research purposes.
- Authorization must be in “plain language.”
- Authorization must be signed and dated by individual or individual's legally authorized representative.
- Specific elements of authorization are required unless waived.
- Individual must receive a signed copy.

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Benefits of E-Consent

- Researchers can go “paperless”
- Researchers can manage the consent process from any location
- Real time analysis of the consent process
  - Subject interactions could be recorded immediately into a tracking system, creating a document trail of timed and dated information regarding the consent process (helpful in a multi-center trial)
- Visual aids can assist subject comprehension
- Subjects can be assessed objectively to see whether they understand the material
- Documentation is more clear (e.g. electronic record of date, time of consent)

Benefits of E-Consent

- Better version control of consent documents, helping to avoid possible non-compliance
- Difficult words can be highlighted and linked to a dictionary to assist subject understanding
- Pages can print out – subject still takes a copy home.
- Videotape recording (e.g. iPad camera) can be implemented to document the consent process.
- If the e-consent is off-site:
  - Less pressure on researchers and subjects
  - No travel reimbursement for consent visit
  - Subjects need not commute to research site
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OHRP Guidance on E-Signatures

- OHRP FAQ on Electronic Signatures: http://answers.hhs.gov/ohrp/questions/7260
  
  “OHRP would allow electronic signature of the document if such signatures are legally valid within the jurisdiction where the research is to be conducted.”

- “OHRP permits IRBs to adopt such technologies … as long as the IRB has considered applicable issues such as how the electronic signature is being created, if the signature can be shown to be legitimate, and if the consent or permission document can be produced in hard copy for review by the potential subject.”

- “If properly obtained, an electronic signature can be considered an “original” for the purposes of recordkeeping.”
State Law Requirements for E-Signature

- Laws on electronic signature vary from state to state.
- Most U.S. states have adopted the “Uniform Electronic Transactions Act.”

FDA: Part 11 Compliance

- 21 CFR 11 (1997) imposes certain requirements on an entity when it chooses to maintain FDA-required records and signatures in electronic form.
- Requirements under Part 11 are intended to ensure the integrity, validity, and trustworthiness of e-records and e-signatures.
  - “Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations.”
FDA: Part 11 Compliance

- FDA Definitions under 21 CFR 11.3(b):
  - (5) **Digital signature** means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.
  - (6) **Electronic record** means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.
  - (7) **Electronic signature** means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

FDA: Part 11 Compliance

- 2007 Guidance for Industry:
FDA: Part 11 Compliance

- 2010 Draft Guidance for Industry:

Secretary's Advisory Committee on Human Research Protections (SACHRP)

Considerations and Recommendations Concerning Internet Research and Human Subjects Research Regulations, with Revisions

Final document, approved at SACHRP meeting March 12-13, 2013
Secretary's Advisory Committee on Human Research Protections (SACHRP)

- "As with other forms of research, the consent/assent process for Internet research should be tailored to the risks and complexities of the research. The absence of direct, in-person contact can add complications to the consent process."

- "Three oft-cited concerns with consent in Internet research are verifying identification, ensuring comprehension, and obtaining appropriate documentation when needed. Adequate identity verification may in some cases be handled by the hosting survey provider; in other cases, with minimal risk research, it may not be a critical issue. Comprehension of the consent materials may be addressed by a checkbox ("I understand and agree") for low risk research, or by mandatory quizzes as a comprehension check. The federal ESIGN law authorizes electronic signatures in certain contexts. In other contexts, state law may control."

Secretary's Advisory Committee on Human Research Protections (SACHRP)

- **Minimal Risk Research:** "The consent process for non-exempt online surveys may include a statement that the subject gives evidence of agreement to participate in the research by ... completing the survey. This is permissible even if the consent document does not include all the elements prescribed at 45 CFR 46.116(a), so long as the IRB approves a waiver or alteration of some elements under 46.116(c) and (d)."

- **Greater than Minimal Risk Research:** "In one example, an industry-sponsored online Phase IV clinical trial, subjects ... had to meet eligibility criteria; those who qualified underwent ID/age verification. Consent documents were then emailed, faxed, or made available on a web site, with additional information provided in audio or video format. Subjects were required to take a comprehension quiz after reviewing the consent materials and had to score 100% to move ahead. A designated contact for questions ... was available to subjects at all times. Applications such as Skype® or LiveChat® have also been used to enable direct communication between researcher and subject during the consent process."
Secretary's Advisory Committee on Human Research Protections (SACHRP)

- **Research Involving Minors**: “There are age verification software products available, which may be of use to researchers. Verification of age can take place through less formal fact-checking embedded in the research instruments (for instance, cross-validating multiple age and birth date questions). Researchers may advertise only on sites that are age limited... Coordinating parental consent with child assent can be difficult, and the Children’s Online Privacy and Protection Act (COPPA) mandates parental permission if subjects under the age of 13 are being recruited and they provide identifiable information.

- **HIPAA Considerations**: “Where the HIPAA Privacy Rule applies, the Rule allows a HIPAA authorization for research to be obtained and signed electronically, provided any electronic signature is valid under applicable law.”

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Is a “Signature” Even Necessary?

- Check the waiver of documentation of consent criteria under FDA and HHS regulations (21 CFR 56.109(c) and 45 CFR 46.117).

- The IRB has the authority to waive documentation of consent (and the signature element of the HIPAA Authorization).
Is a “Signature” Even Necessary?

- Note that under DHHS regulations, there are two sets of criteria in which a study may qualify for a waiver of documentation of consent:
  - 45 CFR 46.117(c)(1) – the only record linking the subject and the research is the consent document and the principal risk of the research is potential harm from a breach of confidentiality
  - 45 CFR 46.117(c)(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
- Under FDA regulations, there is only one criteria in which a study may qualify for waiver of documentation of consent:
  - 21 CFR 56.109(c)(1) – the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context

Money Matters

- Implementing an e-consent process will involve technology and equipment costs as well as changes to policies, procedures, and practices.
- Who pays the cost of implementing the process?
  - Sponsor?
  - Investigator?
  - Institution?
- There are some long-term financial benefits:
  - Paperless – save on paper copies, scanning
  - If e-consent occurs off-site, no need to reimburse travel
  - Better efficiency ("time is money")
- Is it worth the financial risk to implement e-consent, or is it just a fad?
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Useful “Big Picture” Information

Sponsors can keep track of useful information about their multi-center clinical trials in a click.
- Signature Tracking
- Consent Time Tracking
- Demographics
- Site Enrollment Information
Study of chemo-induced neuropathy with six months of symptom surveys and neurologic testing

Informed consent information was provided by either IRB-approved paper consent or iPad-based interactive system (randomized)

Two study samples:
- Clinical Research Professionals
- Patients (non-cancer)

Online survey was completed 18-36 hours later to assess recall of the information provided

Findings:

Consent Time:
- 13.2 min (paper): 22.7 min (iPad)

Information Recall:
- Clinical Research Professionals, n=14
  - 57% correct (paper): 77% correct (iPad)
- Patients, n=55
  - 58% correct (paper): 75% correct (iPad)
  - On the duplicated questions, 63% (paper): 85% (paper)
Web Surveys

- Consent information page appears after an explanation of the research.
- Subject clicks “I Agree.”
  - Note: The study may need to qualify for waiver of documentation of consent. Check with legal counsel on whether “I Agree” is or is not a valid “e-signature” in your jurisdiction.
  - Note: Are the requirements for a valid consent process satisfied in the information sheet?
    - See 21 CFR 50.20 and 50.25 (FDA)
    - See 45 CFR 46.116 (HHS)
    - See Question 34 from FDA Information Sheet at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm (“Is getting the subject to sign a consent document all that is required by the regulations?”)
  - When would a consent discussion over the telephone be needed?
- Subject enters the web survey and completes the survey.

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IRB Review of the Consent Process

- Ensures the regulatory elements are present
- Can waive documentation of consent
- All “subject materials” reviewed (e.g. screen shots)
  - This can be challenging because interactive portions may not be reviewed as a screen shot.
  - There might also be “if, then” contingencies – for example, if there is a quiz, a subject might be prompted back to another part of the consent document.
- “Interactive Review” – IRB reviews the document as it is seen by the subject and review is exhaustive.

Tips for IRB Submissions

- Review state law, and if possible, provide a letter from an attorney in the state to the IRB confirming the e-signature requirements.
- Provide the IRB with an explanation of the consent process in a cover letter.
- Be available to provide a tutorial of the system to reviewing Board members – consider requesting a teleconference or an in-person presentation.
- Be flexible with IRB staff, understanding that your system may be new to the IRB.
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