

Clinical and Translational
Science Institute / **CTSI**
at the University of California, San Francisco



Welcome to Online Training for
Clinical Research Coordinators

ROLE OF THE RESEARCH COORDINATOR

Informed Consent and Informed Consent Process Best Practices
IAW Protection of Human Subjects 21 CFR Part 50
Part 2



Clinical and Translational Science Institute / CTSI
Accelerating Research to Improve Health

UCSF

Objectives

- To describe the terms, requirements, process and documentation standards for study subject's informed consent(s).
- To explain the informed consent process



Elements of Informed Consent

Q: Who is best person to approach subject for the study?

A: Key Personnel

- Principal Investigator
- Person designated by the investigator (e.g. Nurse Practitioner, Sub-Investigator) who is listed on the CHR application
- Appropriately qualified and completed CITI training; has medical knowledge as needed, understanding of adverse effects known to date [Investigator's Brochure, Comparator's Product Label)
- “Team Approach” involves research coordinator as protocol procedure manager to help subject navigate what is expected from their participation.

<http://www.youtube.com/watch?v=A2cjzVINzsc>



UCSF Best Practice

Obtaining Consent of Potential Patients

- PI, NP, Qualified Research Nurse or CNS Responsibilities
- CRC Responsibilities
- Distribution of consent copies, after signatures
- Reference the Delegation of Responsibility and Staff Signature Log
- Utilize UCSF Informed Consent Documentation Form (HUB)
- Surrogate consents, Faxing signed consent, SFVAMC subjects
- Consent process for non-English speaking subjects
 - http://research.ucsf.edu/chr/Guide/chrG_spSpeakWrite.asp#4
 - “Short Form” consent procedure per CHR



Steps to Effective Informed Consent Process

- Discussion of Information by staff listed on CHR application and sponsor delegation log
- Use the latest approved version from iRIS
- Consent and Signature-all fields completed
- Copy given to subject
- Documentation of the Process



When is the Most Appropriate Time to Obtain Consent from a Patient?

Prior to participation in the trial

- **Prior to changing or altering** the potential subject's treatment plan, medications etc.
- **Prior to screening, study-specific procedures**
- **Requires documentation** in the subject's medical and/or research record
 - Date and time informed consent obtained



The Informed Consent Process

Subject has opportunity for “consideration”



*Older adults, children, and patients with cognitive impairments –
-- may require more time --*

- Sufficient time and opportunity to consider whether the prospective subjects ‘wants’ to participate in the study or not
- Talk with family, friends, colleagues, health care providers
- Goal is to minimize coercion or undue influence to participate
- Have copies of the consent without signature to send home with subject so they can mark it up and come back with questions.
- protection of an individual, usually either a child or incapacitated person, in which case the ward is known as a **ward of the court**, or a **ward of the state**.



Consent Considerations

Assessment: Patient Comprehension

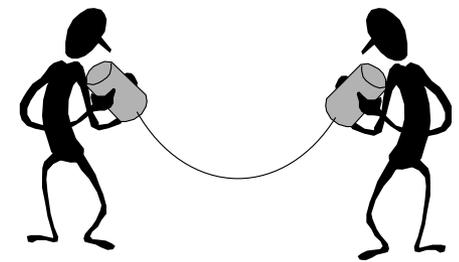
Tell me in your own words

- What is this study about?
- What are the alternative treatment options in this study?
- What will happen to you in this study?
- What do you think you will gain by participating in this study?
- What are the potential adverse events that may happen to you in this study?
- What are the potential risks that may happen to you in this study?



The Informed Consent Process

Language Understandable to Subject



Simple, jargon-free, non-technical language

- 8 tablespoons of blood versus 2 vials of blood
- Generally, 5th-7th grade reading level
- Use term subject vs. patient
- **Avoid coercive or overly reassuring terms or phrases**
 - Promising results to a potential study subject



Translation Practices

Qualified Translators

- Hospital employee, translation service
- Medical expertise
- Proficient in second language
- **Family Members - CAUTION**
 - Inadequate knowledge understanding of medicine and research
 - May not translate verbatim
 - May not share all information (researcher to patient, patient to researcher)
 - Not necessarily 'unbiased'



Non-English Speaking, Illiterate, or Blind Subjects: Planning = Success!

- **Conducting the consent discussion** in the language understandable to the subject and consideration to reading limitations
- **Ongoing communication with the subject:**
 - Throughout the research study
 - In case of emergency
- Plan and standardize your steps for consenting subjects



Non-English Speaking Subjects: Planning = Success!

- Ensure at **least one member of the research team is fluent in the language**, and that research staff member(s) will be available during emergencies.
- Ensure the research team **has 24-hour access to a translation service** with sufficient medical expertise to discuss the research.



Consenting Vulnerable Populations



- Children
- Prisoners
- Mentally disabled
- Visually Handicapped or blind
- Economically or educationally disadvantaged person
- Illiterate persons
- If study is for disease that holds a stigma in society

Tip: check CHR guidelines prior to signing consent for non-English speakers and illiterate subjects.

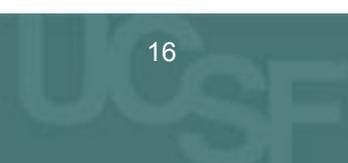


Additional Requirements for Children

- Assessment of risk
- Indications for research in children
- Adequate provisions must be made for **assent**, a child's "affirmative agreement", to participate in research
- **Permission** of parents or guardians (legally authorized representative) is required



Can study related procedures be done prior to obtaining consent from a patient?



The Informed Consent Process

- **No study related procedures/surveys can be administered until the subject signs the consent document.**
- **Agreement to participate is documented by signature**
 - Subject
 - LAR
 - Parent
- **Signature & date requirements**
 - **Personally** signed and dated (by those people noted above)
 - At the time of consent
 - Person conducting discussion
 - Refer to long form (50.27) and short form requirements
 - Witness?
 - Refer to long form (50.27) and short form requirements
- **Recording the Time - not a requirement**
 - Not required in Code of Federal Regulations but has become an industry standard (best practice)



The Informed Consent Process

Subject receives copy of Informed Consent Document

- ICH requires signed copy
- FDA regulation does not require a signed copy to be given to subject
- Filing: Follow UCSF Policy for Filing signed copies of Informed Consent in APEX and documentation of consent process
- **Best Practice:** provide copy of informed consent, signed, dated and complete



What is the FDA Looking for in the Patient Source Documentation?

- **What needs to be documented in the case history source record?**
 - Case history for each individual shall document informed consent was obtained prior to study participation
 - **IAW FDA Requirements 21 CFR 312.62 (b)**



What Needs to be Documented in the Case History - Source Record?

- ✓ Discussion with subject of information in the **informed consent**.
- ✓ Questions were **answered**.
- ✓ Patient **comprehension**.
- ✓ If oral consent is given, Who was **present** during the consent **to act as witness**.
- ✓ No **study procedures** were done prior to signing of the consent



What Needs to be Documented in the Case History - Source Record?

- ✓ Name of translator, when needed, and affiliation/translator service.
- ✓ Signed and dated by the person obtaining consent and subject or legally authorized representative (LAR).
- ✓ Copy of the signed and dated consent was given to the subject or LAR
- ✓ Subject re-consented when new risks or new treatment/benefits are discovered.



'Ongoing' Informed Consent During the Study

New Information

- Must be added
- Modification of the ICD
 - Adverse events related to study
 - Serious adverse events ; blindness related to study
 - Change to study procedures, length of time on study.
- *What does signing a modified Informed Consent Document indicate?*
 - **Continued** willingness to participate in light of
 - Safety profile changes; increased risk
 - Change in subject's rights
 - Change in study procedures (e.g. protocol amendments)



Can you Alter the Informed Consent Form after it has Been Signed?

NO, subject would need to be re-consented



FDA Investigator Warning Letters-Consents

What not to do.....

2. You failed to obtain legally effective informed consent [21 CFR part 50 and 21 CFR 312.60].

Except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative [21 CFR 50.20]. Informed consent must be documented by the use of a written consent form approved by the institutional review board (IRB) and signed and dated by the subject or the subject's legally authorized representative at the time of consent [21 CFR 50.27(a)]. You also failed to obtain proper assent as determined to be appropriate by the IRB [21 CFR § 50.55].

a. Fabricated signatures of the subject's legally authorized representative were found on the consent forms for subjects [(b)(6)], who were enrolled in protocol [(b)(4)], and subject [(b)(6)], who was enrolled in protocol [(b)(4)]. We note that you discovered the fabricated signatures through your own internal audit, and that you sent letters dated September 10, 2007 to the parents of subjects [(b)(6)], and a letter dated December 11, 2007 to the representatives of subject [(b)(6)], requesting that the informed consent documents be signed again. In addition, you promptly reported the findings to the IRB. In your May 22, 2008 response to the Form FDA 483, you stated that you asked the study coordinator to ensure that copies of the original, signed consent forms were placed in the subjects' medical records, according to institutional policy, but you did not confirm this action. You stated that had this occurred, you would have been able to retrieve a copy of the original consent forms. You stated that it is presumed that your former research nurse (study coordinator) apparently falsified the signatures after she lost the original, signed consent forms. You also stated that you reported these findings to the Board of Registration in Nursing. As the clinical investigator, you are responsible for oversight of study activities delegated to study staff.



Based on the times recorded for appointment time, sign-in, and the commencement of protocol procedures, it does not appear possible that you obtained legally effective informed consent from the subjects in the chart below, in compliance with 21 CFR 50.20 and 50.27. This is because either 1) study-related procedures are listed as having taken place prior to the scheduled appointment time and/or prior to the time the subject signed in, or 2) based on the study records, the time between the appointment time, the time the subject signed in and/or the commencement of the procedure(s) did not provide adequate opportunity for the subjects to read the informed consent document, and to consider whether or not to participate in the study, before signing the informed consent form. For example, Subject **[(b)(6)]** was enrolled into the study on March 25, 2006. The sign in sheet notes that Subject **[(b)(6)]** arrived at your site at 9:00 a.m. However, source documents showed that study related procedures were performed prior to the subject's arrival (i.e., a blood sample was drawn at 8:50 a.m. In addition, as detailed below

Subject	Date Informed Consent Obtained	Sign-In Date	Sign-in Time	Appointment Time	Blood Pressure Measured	Blood Samples Taken	ECG Conducted
[(b)(6)]	Unclear from records	3/23/06	9:38 a.m.	9:30 a.m.	9:20 a.m.	9:40 a.m.	9:35 a.m.
[(b)(6)]	3/23/06	3/23/06	9:38 a.m.	9:30 a.m.	9:00 a.m.	9:20 a.m.	9:15 a.m.
[(b)(6)]	7/20/06	7/20/06	9:48 a.m.	10:00 a.m.	8:30 a.m.	9:30 a.m.	8:44 a.m.
[(b)(6)]	8/8/06	8/8/06	9:11 a.m.	9:30 a.m.	9:05 a.m.	9:45 a.m.	8:20 a.m.
[(b)(6)]	8/16/06	8/16/06	No time indicated; most likely between 9:00 a.m. and 9:30 a.m. based on other patients' recorded sign-in times that day	No time indicated	8:38 a.m.	8:53 a.m.	8:50 a.m.

VIOLATIONS RELATED TO INVESTIGATOR RESPONSIBILITIES [21 CFR 312.60, 312.66, 312.62(a), and 312.62(c)]

1. You failed to obtain informed consent of subjects involved in research in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].

21 CFR 50.20 requires that except as provided in sections 50.23 and 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. In addition, the FDA regulations require that informed consent be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent [21 CFR 50.27(a)].

a. There were no signed and dated informed consent documents on file for subjects [(b)(6)] and [(b)(6)] enrolled in study [(b)(4)]

b. There is no signature of the subject or the subject's legally authorized representative on the informed consent document for subject [(b)(6)] enrolled in study [(b)(4)] at the 8/31/00 visit.

c. There is no signature of the subject or the subject's legally authorized representative on the informed consent document for subject [(b)(4)] enrolled in study [(b)(4)] for the follow-up visit on 1/14/03.

d. Regarding study [(b)(4)], study procedures were conducted prior to obtaining informed consent from subjects [(b)(4)] and [(b)(4)]. Specifically, for subject [(b)(4)], an MRI of the brain was conducted on 10/4/88, but informed consent was not signed by the subject until 10/06/88. For subject [(b)(4)], a liver biopsy was performed on 10/4/94, but informed consent was not signed by the subject until 10/5/94.

e. The information that was given to the subject or the subject's legally authorized representative was not in a language understandable to the subject or the subject's legally authorized representative. Specifically, non-English speaking subjects were given informed consent documents written in English. Examples include, but are not limited to, the following: Subjects [(b)(6)] enrolled in study [(b)(4)] and subjects [(b)(6)] enrolled in study [(b)(4)]



1. You failed to obtain informed consent of the subjects to whom the study drug was administered [21 CFR § 312.60; 21 CFR. § 50.20].

Section 4.2 of Protocol **[redacted]** required that subjects sign the informed consent document (ICD) to indicate they understood the purpose of the study and procedures. The protocol also stated that subjects would be excluded if they could not provide their own consent. The investigation found that a guardian signed the ICD for Subject **[redacted]** on February 20, 2006. The sponsor recommended this subject be immediately discontinued from the study for consenting reasons on April 18, 2006.

 Your response letter dated June 6, 2006 did not address the issue of consent related to Subject **[redacted]**. Your letter did address the issue of informed consent related to Subject **[redacted]**. This subject consented to the open-label phase of the study while hospitalized and suffering periods of delusion. You assert that this subject's consent was valid in part because the subject had been informed of the open-label phase of the trial at the time the subject first consented to trial participation. This assertion is improper. Knowledge of trial phases does not suffice to demonstrate informed consent to those phases. Moreover, a subject can withdraw consent at any time during a study, which underscores the fact that informed consent must be established independently at each trial phase required under the protocol [21 CFR § 50.25(a)(8)].

1. You failed to obtain informed consent of each human subject in accordance with 21 CFR 50 [21 CFR 312.60].

Specifically, 21 CFR 50.20 states that except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. In addition, except as provided in 21 CFR 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB [21 CFR 50.27(a)].

The following violations were noted in reference to Protocol **[redacted]**

a. Four of 23 subjects (**[redacted]**) had protocol-specified baseline laboratory blood samples drawn prior to signing and dating the informed consent document.

b. The IRB approved informed consent document required documentation of the actual time in which legally effective informed consent of the subject was obtained. There was no documentation of the actual time in which subjects **[redacted]** signed and dated the consent forms. In addition, we were unable to verify that these subjects signed and dated the informed consent forms prior to any protocol specified procedures being conducted on them.

In your September 18, 2007 written response, you noted that in all cases the subject had been verbally consented prior to any study procedures being performed. Verbal consent, however, is inadequate. The exceptions in 21 CFR 50.23 and 21 CFR 50.24 to the informed consent requirements, as well as the exception in 21 CFR 56.109(c) to use of the written consent form approved by the IRB, did not apply to the conduct of this study.

1. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 [21 CFR 50.20 and 50.27(a)].

Investigators are responsible for ensuring that informed consent is obtained using an IRB-approved consent document prior to performance of any study-related procedures. The IRB approval letter for this study, dated March 7, 2000, provided you with a copy of the consent form with the date of the IRB approval stamped on it, and stated, "Please use this copy of the consent form with the IRB approval date and make additional copies as they are needed." You failed to ensure that the current, IRB-approved, version of the informed consent was executed by each of the subjects prior to their participation in the study. Examples of this failure include, but are not limited to, the following:

- a.) Two of the **[redacted]** subjects you enrolled and randomized into the study signed an unapproved version of the consent form. The IRB-approved informed consent form was a 4-page document stamped with "IRB Mar 7 2000" on the first page, and required the signatures of the study subject, a witness, and the principal investigator. The forms signed by Subjects **[redacted]** and **[redacted]** were 2-page documents that were substantially different from the IRB-approved version.
- b.) Subject **[redacted]** signed a consent form that did not contain the IRB approval stamp.

3. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60 and 21 CFR 50].

Subject 8210 was randomized to protocol [(b)(4)] on June 12, 2006. You did not obtain informed consent from this subject until June 26, 2006.

e. Informed consent documents were dated by study personnel rather than the legally authorized representative for subjects [(b)(4)] enrolled in protocol [(b)(4)], and subject [(b)(4)] enrolled in protocol [(b)(4)]. In your May 22, 2008 response to the Form FDA 483, you acknowledged that it was your routine practice to insert the date yourself, prior to the parents' signatures, in order to simplify the process. You stated that you now know that subjects and parents must date the consent forms themselves. We acknowledge your assurance that corrective actions have been



Warning Letter Corrective Action Plan

- Pick a **two** of the problems identified in the last slides from an FDA inspection.
- List solutions you would implement to correct them if this were your site.



Notes

- ---
- ---
- ---
- ---
- ---



Takeaways.....

Subject Protection as codified in the Belmont Report

- Informed consent process...
 - Voluntary
 - Subject understands and comprehends the impact of their participation in the clinical trial
 - Information exchange with question and answers
 - Prior to collecting data or engaging the subject in research procedures.
- Ongoing communication of risks, benefits, willingness to participate
 - Updates, revisions during study require re-consenting if it impacts the prior study subjects
 - Keep a consent log for each study: Add Amended consent approval date and when each subject was re-consented
 - Document that new added risks were explained



Takeaways.....

Informed consent is not just signing a form: it is a process

- Development of consent document conforming to CHR templates and other templates provided by the sponsor of the study
- Verbal consent or Written consent as needed for type of subjects being recruited
- Non-English speaking subjects need translated consent forms; these are also approved by IRB
- Agreement noted by a documented signature on the informed consent document
- Person consenting must be listed as key personnel on the CHR application.

