

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



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

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UCSF

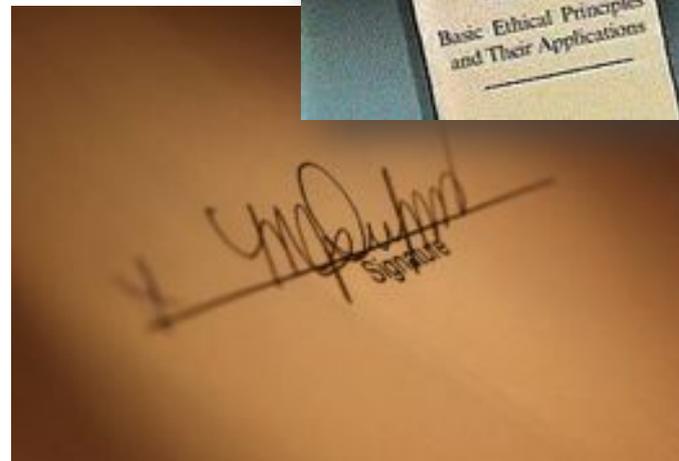
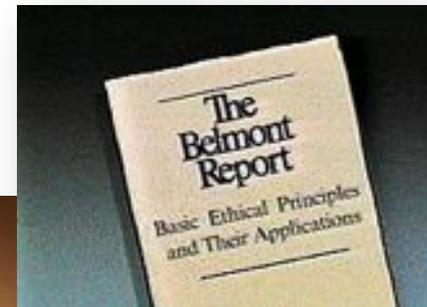
Objectives

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



Ethical Standard for Subject Informed Consent

- *“Extent and nature of information should be such that persons ... can decide whether they wish to participate...”*
 - 21 CFR Part 50.20, 50.25, 50.27
- Belmont Report
 - Beneficence
 - Respect
 - Justice



Required Elements of Informed

Information that must be provided to the subject and included within the consent document.

- Introduction
- Study involves research
- Purpose of research
- Duration of subject involvement in the study
- Description of study procedures
- Identification of any experimental procedures
- Potential risks/ discomforts
- Potential benefits to subjects or others



More *Required* Elements of Informed Consent

- Alternative procedures or treatments (that are already available to the potential subject)
- Confidentiality of subject records (e.g. access to sponsor, FDA)
- Compensation for injury and treatment in event of emergency
- Who subject can contact
- Participation is voluntary

New-March 7, 2012: “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.”



Additional Elements of Informed Consent

- Unforeseen risks statement
- Reasons for involuntary termination
- Additional costs to subject
- Consequences of decision to withdraw (e.g. impact on their health, treatment, personal welfare etc.)
- New findings will be communicated
- Approximate number of subjects in the study
- *Payments to the subject are to be included in the document and when they will be paid (e.g. incentive, travel costs etc.)**



Key Terms Associated with Consent of Subjects

- Clinical investigation, study, or protocol
- Investigator and Key Personnel with ability to explain the study to the subject, document consent process
- Human subject
- Institutional Review Board
- **Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” See the Common Rule at <http://www.hhs.gov/ohrp/humansubjects/>



Key Terms Associated with Consent of Subjects

- **Legally authorized representative (LAR)** means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (45 CFR 46.102(c)) IRBs may wish to consult with legal counsel when deciding who can serve as an LAR for subjects of proposed research. **Healthcare Power of Attorney**
- Family member may or may not be an LAR.
- Assent is consent document for subjects under 18 years old; all minors are asked for assent but parents' legal consent can overrule minor's refusal.
- Ward is someone placed under the protection of a legal guardian. A court may take responsibility for the legal 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**.
- A **legal guardian** is a person who has the legal authority to care for the personal and property interests of another person, called a ward.



Key Terms Associated with Consent of Subjects

Health Information Portability and Accountability Act (HIPAA) is not a consent but a separate document or authorization signed by the subject to allow researchers access to personal health information (PHI) per the HIPAA Privacy Rule of US Dept. of Health and Human Services.

- **IF you know who your subject is..HIPAA authorization is required.**
- **IF you or others could find out who the subject is using date of birth or hospital numbers...HIPAA authorization is required.**
- **Violation of the HIPAA Privacy Rule is subject to state and federal law and includes fines.**

What research does not require a signed HIPAA authorization?

- Study granted a waiver of consent/authorization by CHR/IRB approval
- Research using completely de-identified data; often already collected and stored in an anonymously
- Research using a limited data set excluding PHI



Key Definitions Associated with Consent of Subjects



Experimental Research Subject's Bill of Rights

California law, under Health & Safety Code '24172, requires that any person asked to take part as a subject in research involving a medical experiment, or any person asked to consent to such participation on behalf of another, is entitled to receive a copy of these Bill of Rights **written in a language in which the person is fluent.**

Please visit http://www.research.ucsf.edu/chr/Guide/chrB_BoR.asp for more information and a list of over 20 translations, including access to a copy in Braille.

Documentation of this can be an original copy kept with the signed informed consent or you can create a note signed by the investigator as part of the consent process. The law requests this list be given prior to discussing the study informed consent



HIPAA Authorization Waivers

- PI and IRB must certify that research:
 1. Could not practicably be conducted w/o waiver
 2. Could not practicably be conducted w/o protected health information (PHI)
 3. Poses minimal risk to privacy based on written assurance that the PHI will not be reused or disclosed and that there is an adequate plan to protect identifiers.
- To accomplish this, PI fills out Waiver of Consent/Authorization Form available on the [CHR website](#) and submits with application
- Research released by a waiver must be tracked for disclosure to the subject



What is the Role of the ‘Impartial Witness’ in the Informed Consent Process?

ICH E-6 GCP* 1.26 Impartial Witness:

“A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject’s legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject”

*ICH E-6 is the International Conference on Harmonization, document E-6, explaining Good Clinical (Research) Practice.



Written Consent General Guidelines

What is submitted to the UCSF IRB as regulatory documents?

- Obtained from subject or legally authorized representative (health care power of attorney, spouse)
- For a minor: parental consent (one or both) and assent of child, unless child emancipated
- No exculpatory language
- Obtained before any study procedures are performed on the subject
- Documentation in the subject's medical/research record the process of discussion and risks and documents given to subject.



FDA Inspection Findings of Consent Violations

- Enrolled without any documentation of informed consent through the use of an IRB approved consent form
- Study assessments and screening procedures conducted on screening visit, prior to consent being *signed*
- Subject signed an outdated version of consent
- Subject randomized prior to consent
- Failure to re-consent subjects using the correct revised consent form per IRB requirements
- Failure to obtain assent as deemed an IRB requirement



More FDA Inspection Violations

- Subject signed a sub-study consent but not the consent for the main study.
- Subject representatives documented as being non-English speaking; they signed an English informed consent.
- Consent form indicated use of placebo; however, the study did not use a placebo.
- Site staff fabricated LAR signatures.
- No documentation that a copy of the consent was provided to the subject.
- Subjects did not date the informed consent form.



FDA Inspections Compliance Program Guidance Manual (CPGM 7348.811)

FOOD AND DRUG ADMINISTRATION
COMPLIANCE PROGRAM GUIDANCE MANUAL

PROGRAM 7348.811

PROGRAM 7348.811

CHAPTER 48- BIORESEARCH MONITORING

CLINICAL INVESTIGATORS AND SPONSOR-INVESTIGATORS

Date of Issuance: December 8, 2008

Guidance for FDA Staff

SUBJECT: Clinical Investigators and Sponsor Investigators		IMPLEMENTATION DATE December 8, 2008
REVISION:		COMPLETION DATE Continuing
DATA REPORTING		
PRODUCT CODES	PROGRAM ASSIGNMENT CODES	
FACTS does not require product codes for Bioresearch Monitoring Inspections	09811 Food Additives	
	41811 Biologics (Cell; Gene Transfer)	
	42811 Biologics (Blood)	
	45811 Biologics (Vaccines)	
	48811 Human Drugs	
	68811 Animal Drugs	
	83811 Medical Devices	

FIELD REPORTING REQUIREMENTS:



FDA Inspections CPGM 7348.811

F. HUMAN SUBJECTS' RECORDS

1. Informed Consent

a. Describe the informed consent process.

For the study being inspected, include the following information:

Current changes (ED: Retain "current changes" only in sections where changes made)

DATE OF ISSUANCE 12/08/08
FORM FDA 2438₂ (electronic-09/2003)

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- i. Who (investigator, nurse, study coordinator, etc.) explained the investigational study and consent document to prospective study subjects, and was it provided in a language understandable to each subject?
- ii. How did the informed consent process take place? (e.g., was this explanation given orally, by video, through a translator, etc.)?
- iii. Was consent obtained prior to enrollment in the study (i.e., prior to performance of any study related tests and administration of the test article)?
- iv. After signing and dating the informed consent document, was each subject or the subject's legally authorized representative given a copy of the consent document?
- v. Was the appropriate IRB-approved version of the informed consent document used for all subjects?



FDA Inspections CPGM 7348.811

- vi. If the short form was used (per 21 CFR 50.27(b)(2)), was the informed consent process appropriately documented?
 - a. Did the subject or the subject's representative sign the short form?
 - b. Was a witness present, who signed the short form and the copy of the summary?
 - c. Did the person actually obtaining the consent sign a copy of the summary?
 - d. Is the case history documented to show whether a copy of the summary and the short form were given to the subject or the subject's representative?

- vii. **Review** the IRB approval letter for the study. Did the IRB stipulate any conditions for the informed consent process and, if so, did the clinical investigator follow those instructions/stipulations?



FDA Inspections CPGM 7348.811

b. **Review** the informed consent documents signed by the subjects. If the number of subjects at the site is relatively small (e.g., 25 or fewer subjects), review 100% of the informed consent documents. For larger studies, a representative number of informed consent documents should be reviewed (for example, may be specified in a sampling plan provided with the assignment).

Determine the following:

- i. Did the subject or the subject's legally-authorized representative sign the informed consent document prior to entry into the study? If the subject did not sign the informed consent document, **determine** who signed it and that person's relationship to the subject. **Describe** how the clinical investigator determined that the person signing the informed consent document was the subject's legally-authorized representative.

Current changes (ED: Retain "current changes" only in sections where changes made)

DATE OF ISSUANCE 12/08/08
FORM FDA 2438₂ (electronic-09/2003)

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- ii. Whether subjects signed the version of the informed consent document that was current at their time of entry into the study.
- iii. For pediatric studies, was assent obtained from the subjects in addition to the permission of the parents?
- iv. Whether the written consent document(s) or oral consent complies with the eight (8) required elements in 21 CFR 50.25(a).



FDA Inspections CPGM 7348.811

- If any problems are found (e.g. investigator failed to obtain consent from one or more subjects, consent was not obtained prior to enrollment in the study, investigator failed to use the correct informed consent document, etc.), the sample should be expanded to determine the extent of the problem.
- Collect documentation to support each observation.
- Report the total number of informed consent documents that were reviewed and the number of documents exhibiting the problem.



FDA Investigator WARNING LETTERS

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	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.

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

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

