Introduction

The purpose of this clinical research guidebook is to provide researchers at UC Davis with a road map to navigate the processes and procedures for conducting clinical research at UC Davis. The guidebook can also serve as reference for investigators and site staff as to the federal regulations governing clinical research in the United States. Although we have purposely not provided extensive information about all regulations governing human research, throughout the guidebook we have cited specific regulations and websites where more information can be found. In addition, UC Davis employs the Collaborative Institutional Training Initiative (CITI) program which is a web based training program to satisfy the training requirement for all research personnel conducting human subjects research under the auspices of UC Davis. Certifications are valid for 3 years. This course also provides an extensive amount of information on the regulations governing research with human subjects. For more information, please check the website at: https://www.citiprogram.org

The guidebook is divided into several sections organized to help the investigator and site staff navigate through the various requirements of clinical research at UC Davis. The guidebook is not meant to be all inclusive and investigators and site staff can always find more help from the UC Davis Clinical and Translational Science Center (http://www.ucdmc.ucdavis.edu/ctsc/), the UC Davis IRB (http://research.ucdavis.edu/u/a/irb), and Health System Compliance (http://www.ucdmc.ucdavis.edu/compliance/).

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CHAPTER 1: Regulations Affecting Clinical Research: Federal Agencies

Department of Health and Human Services (HHS) is the government’s principle agency for protecting the health of all Americans. It comprises several public health services agencies including the FDA (Food and Drug Administration), OHRP (Office of Human Research Protection), the NIH (National Institutes of Health), and the Centers for Medicare and Medicaid Services (CMS).

The Food and Drug Administration (FDA) is an agency of the United States Department of Health and Human Services. The FDA is responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products, and cosmetics.

The Office of Human Research Protection (OHRP) provides leadership, guidance, and education in the protection of the rights, welfare, and well being of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP performs these services through providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and regulatory issues in biomedical and social-behavioral research.

The National Institutes of Health (NIH) seeks to provide fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. As part of this mission NIH provides leadership and direction to programs designed to improve health and provides support for research.

Centers for Medicare and Medicaid Services (CMS) is the US Federal agency, which administers Medicare, Medicaid, and the Children’s Health Insurance Program. On June 7, 2000, the President of the United States issued an executive memorandum directing the Secretary of Health and Human Services to “explicitly authorize [Medicare] payment for routine patient care costs...and costs due to medical complications associated with participation in clinical trials.” CMS responded to the executive order with the clinical trial policy national coverage determination (NCD). Medicare State Fiscal Intermediaries also issues Local Coverage Determinations (LCD). For California, our intermediary is Palmetto GBA. See Section “Regulations Affecting Clinical Research: Center for Medicare Services” for Medicare regulations of clinical research billing.
Code of Federal Regulation (CFR)

The **Code of Federal Regulations** (CFR¹) comprises the general and permanent rules and regulations published in the Federal Register by the Federal executive departments and agencies. The CFR is divided into 50 titles that represent broad areas subject to Federal regulation. Title 45 CFR encompasses regulation of Public Welfare. Title 21 CFR is administered by the FDA and covers regulations of Food and Drugs.

**Title 45 CFR 46 (The Common Rule)**

In 1991, the core HHS regulations (45 CFR Part 46, Subpart A) were formally adopted by more than a dozen other Departments and Agencies that conduct or fund research involving human subjects as the Federal Policy for the Protection of Human Subjects, or “Common Rule.” In the same year, the Department of Veterans Affairs promulgated this same rule at 38 CFR Part 16. Today, the 1991 Federal Policy is shared by 17 Departments and Agencies, representing most, but not all, of the federal Departments and Agencies sponsoring human-subjects research.

The main elements of the Common Rule include:

- requirements for assuring compliance by research institutions;
- requirements for researchers obtaining and documenting informed consent;
- requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping;
- additional protections for certain vulnerable research subjects – pregnant women, prisoners, and children.

¹ [http://ecfr.gpoaccess.gov](http://ecfr.gpoaccess.gov)
As written, **45 CFR 46** applies only to federally supported research. However, most universities, including UC Davis, maintain an agreement called the Federalwide Assurance (FWA) with Department of Health and Human Services (HHS) that extends the protections of **45 CFR 46** to all research conducted by University personnel, regardless of the source of funding, or lack thereof. The FWA is required before the institution may receive federal research funds.

To view the regulations, visit the Office for Human Research Protections (OHRP) of the Department of Health and Human Services (DHHS) website.²

**Title 21 CFR**

The FDA regulations (**Title 21 CFRs**) are applicable when research is being conducted to develop a medical product that will be licensed for sale in the United States.

Certain federally sponsored and privately sponsored research is subject to the regulations of the FDA at 21 CFR Parts 50 and 56. FDA regulations confer protections on human subjects in research when a drug, device, biologic, food additive, color additive, electronic product, or other test article subject to FDA regulation is involved.

**Overall comparison of FDA and HHS Regulations for Protection of Human Subjects**

FDA regulations and the provisions of the Common Rule are largely congruent, although some significant differences exist.

The HHS regulations [**45 CFR Part 46**] apply to research involving human subjects conducted by the HHS or funded in whole or in part by the HHS (i.e., NIH). FDA regulations [**21 CFR parts 50 and 56**] apply to research involving products regulated by the FDA. Federal support is not necessary for the FDA regulations to be applicable. When research involving products regulated by the FDA is funded, supported or conducted by FDA and/or HHS, both the HHS and FDA regulations apply.

**Institutional Review Boards**

An **institutional review board (IRB)**, also known as an **independent ethics committee (IEC)** or **ethical review board (ERB)**, is a committee that has been formally designated by the research institution to approve, monitor, and review

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² [http://www.hhs.gov/ohrp](http://www.hhs.gov/ohrp)
biomedical and behavioral research involving humans with the aim to protect the rights and welfare of the research subjects. In the United States, the Food and Drug Administration (FDA) and Department of Health and Human Services (specifically Office for Human Research Protections) regulations have empowered IRBs to approve, require modifications in planned research prior to approval, or disapprove research. An IRB performs critical oversight functions for research conducted on human subjects that are scientific, ethical, and regulatory.

In the United States, IRBs are governed by Title 45 CFR Part 46 and 21 CFR 56 (for FDA-regulated trials). These regulations implement provisions of the National Research Act of 1974, defining IRBs and requiring them for all research that receives support, directly or indirectly, from what was the Department of Health, Education, and Welfare (now the HHS). IRBs are themselves regulated by the Office for Human Research Protections (OHRP) within HHS. IRBs were developed in direct response to research abuses earlier in the twentieth century. Independent or commercial IRBs have responsibilities identical to those based at academic or medical institutions (local IRBs), and they are governed by the same federal regulations.

The composition of an IRB for the FDA’s requirements is set in 21 CFR 56.107 and 45 CFR 46.107.

(a) The IRB must have at least five members. The members must have enough experience, expertise, and diversity to make an informed decision on whether the research is ethical, informed consent is sufficient, and appropriate safeguards have been put in place. If the IRB works with studies that include vulnerable populations, the IRB should have members who are familiar with these groups. It is common for an IRB to include an advocate for prisoners when considering research that involves them.

(b) The IRB should include both men and women, as long as they aren’t chosen specifically for their gender. The members of the IRB must not be all of the same profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. These terms are not defined in the regulations.

(d) The IRB must include at least one person who is not affiliated with the institution or in the immediate family of a person affiliated with the institution. These are commonly called “Community Members.”

(e) IRB members may not vote on their own projects.

(f) The IRB may include consultants in their discussions to meet requirements for expertise or diversity, but only actual IRB members may vote.
For information on UC Davis local IRB, please see section **UC Davis IRB Committees, p. 54.**

Review of Research by IRBs
Adapted from (**45 CFR 46.109**)  

(a) An IRB reviews and have authority to **approve, require modifications in** (to secure approval), or **disapprove** all research activities.

(b) An IRB requires that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB’s judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB requires documentation of informed consent or may waive documentation in accordance with §46.117.

(d) An IRB notifies investigators and the institution in writing of its decision to approve or disapprove the proposed research activities or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it includes in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB conducts continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and has authority to observe or have a third party observe the consent process and the research.

References
HHS (http://www.hhs.gov)  
FDA (http://www.fda.gov)  
OHRP (http://www.hhs.gov/ohrp/)  
NIH (http://www.nih.gov)  
CMS (http://www.cms.gov)  
Title 45 CFR (http://ohsr.od.nih.gov/guidelines/45cfr46.html#)  
Title 21 CFR (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm)
CHAPTER 2: Regulations Affecting Clinical Research: Informed Consent

What is Informed Consent?

Informed Consent* is the process of communication between a patient and physician that results in the patient’s authorization or agreement to undergo a specific medical intervention (from American Medical Association, 1998). ...It’s more than a signature on a piece of paper!

The informed consent process is just one part of a larger system in place to safeguard participants who voluntarily participate in research projects to study new practices that may improve treatment, supportive care, screening, and disease prevention. It ensures that clinical research studies are conducted ethically, and without undue risk to participants.

The informed consent process provides the participant with ongoing explanations that will help them make educated decisions about whether to begin or continue participating in a trial.

- Obtaining informed consent is the provider’s legal responsibility. Failure to obtain informed consent renders any U.S. physician liable for negligence or battery and constitutes medical malpractice.
- Granting informed consent is the patient’s exclusive right.

Steps of the Informed Consent Process include:

- A clear discussion of the information in the Informed Consent Form
- A signed and dated Informed Consent Form
- Source document containing a progress note/chart note

Rather than an endpoint, the consent document should be the basis for a meaningful exchange between the investigator and the subject.

*Reference: 21 CFR 50
Informed Consent is required, if the study involves:
• human participation
• greater than minimal risk
• use of human organs, tissue or biological fluids
• clinical data or other sensitive personal information

Informed Consent is not required, if the study involves:
• Observation of legal public behavior
• Study of existing publicly available data/records
• Normal educational practices
• Where the researcher does not manipulate the subjects’ behavior and the study does not involve more than minimal risk.
• Surveys and questionnaires involving perception, cognition, or game theory and do NOT involve gathering personal information, invasion of privacy or potential for emotional distress.

Waver of Informed Consent may be given if:
• The research involves no more than minimal risk to the subjects
• The waiver or alteration will not adversely affect the rights and welfare of the subjects
• The research could not practicably be carried out without the waiver or alteration
• Whenever appropriate, the subjects will be provided with additional pertinent information after participation

Subjects should be consented prior to:
• Screening procedures performed solely for eligibility determination
• Altering the subject’s care for the purposes of research

Consent Document Content

For studies that are subject to the requirements of the FDA regulations, the informed consent documents should meet the requirements of 21 CFR 50.20 and contain the information required by each of the eight basic elements of 21 CFR 50.25(a), and each of the six elements of 21 CFR 50.25(b) that is appropriate to the study. IRBs have the final authority for ensuring the adequacy of the information in the informed consent document.

21 CFR 50.20 points out that except as provided in 21CFR 50.23 and 21CFR 50.24, an investigator may not 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. Importantly 21 CFR 50.20 also states:
• An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence;
• The information that is given to the subject or the representative shall be in language understandable to the subject or the representative;

• No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Eight Required Elements of the ICF:

1) A clear statement that the study involves “research”;
   a. An explanation of the purposes of the research;
   b. The expected duration of the subject’s participation;
   c. A complete description of the procedures to be followed, and identification of procedures that are performed as standard of care and identification of procedures that are performed solely for the purposes of research;

2) A description of the reasonably foreseeable risks and discomforts;

3) A description of any benefits to the participant or others that may reasonably be expected from the research;

4) A disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the participant;

5) A description of the extent to which confidentiality of records identifying the participant and privacy will be maintained and for FDA-regulated research, including a statement that notes the possibility that the FDA might inspect the records;

6) An explanation as to whether any compensation, as well as whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained;

7) An explanation of whom to contact for answers to pertinent questions and to voice comment or concerns about the research (e.g., Investigator or the IRB, or the IRB Administration) and research participants’ rights (e.g., information available from IRB Administration Office, or on IRB Administration website), and whom to contact (as well as an alternate contact information) in the event of a research-related injury to the participant; and

8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled, and without being required to provide any reason for their decisions.
Additional Elements of the ICF (required if applicable):

1) Whenever the research involves investigational articles or interventions whose risk profile is not well known: a statement that the particular treatment or procedure may involve risks to the participant, which are currently unforeseeable;

2) Whenever the research involves pregnant women or women of child bearing potential and involves interventions whose effects on fetuses are not well known: a statement that if the participant is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable;

3) Whenever there are anticipated circumstances under which the participant’s participation may be terminated by the investigator without regard to the participant’s consent: List anticipated circumstances under which the subject’s participation may be terminated by the Investigator without regard to the participant’s consent;

4) If there is the potential that costs of research procedures will not be paid by the sponsor or the participant’s insurance, a description of any additional costs to the participant that may result from participation in the research should be in the consent document;

5) Whenever there are adverse consequences to a decision to withdraw from the research: the consequences of a participant’s decision to withdraw from the research should be included;

6) Procedures for orderly termination of participation by the participants should be included whenever such procedures are included in the research;

7) A statement that significant new findings developed during the course of the research which may relate to the participant’s willingness to continue participation will be provided to the participant should be included whenever such information is likely to be developed during the course of the research;

8) The approximate number of participants involved in the study should be included whenever such information may affect a participant’s willingness to take part in the research;

9) The probability of random assignment to placebo or to each treatment should be included for all randomized trials; and

10) The IRB may require that information, in addition to that required in Federal regulations, be given to research participants when in its judgment the information would meaningfully add to the protection of the rights and welfare of participants.

See Appendix 2 for helpful tips on preparing the Consent Elements.
The IRB should ensure that technical and scientific terms are adequately explained, and that complex scientific concepts are properly converted into simple concepts that the typical subject can read and comprehend.

Although not prohibited by the FDA regulations, use of the wording, “I understand...” in informed consent documents may be inappropriate as many prospective subjects may not fully “understand” the scientific and medical significance of all the statements. Consent documents are more understandable if they are written just as the clinical investigator would give an oral explanation to the subject, that is, the subject is addressed as “you” and the clinical investigator as “I/we.” This writing style also helps to communicate that there is a choice to be made by the prospective subject. Use of first person may be interpreted as presumption of subject consent, i.e., the subject has no choice. Also, the tone of the first person “I understand” seems to misplace emphasis on legal statements rather than on explanatory wording enhancing the subject’s comprehension.

Subjects are not in a position to judge whether the information provided is complete. Subjects may certify that they understand the statements in the consent document and are satisfied with the explanation provided by the consent process (e.g., “I understand the statements in this informed consent document.”) They should not be required to certify completeness of disclosure (e.g., “This study has been fully explained to me,” or, “I fully understand the study.”)

The FDA discourages use of phrases such as, “FDA has given permission...” or “FDA has approved...” in consent documents. Technically, the FDA does not “approve” drug studies under an IND (Investigational New Drug) Application. FDA does approve device studies under IDE (Investigational Device Exemption).

Consent documents should not contain unproven claims of effectiveness or certainty of benefit, either explicit or implicit, that may unduly influence potential subjects. Overly optimistic representations are misleading and violate FDA regulations concerning the promotion of investigational drugs [21 CFR 312.7] or investigational devices [21 CFR 812.7(d)] as well as the requirement to minimize the possibility of coercion or undue influence [21 CFR 50.20].

The FDA believes that an explicit statement that an IRB has approved solicitation of subjects to participate in research could mislead or unduly induce subjects. Subjects might think that, because the IRB had approved the research, there is no need to evaluate the study for themselves to determine whether or not they should participate.

The informed consent documents may not contain any exculpatory language through which the participant is made to waive or appear to waive any of the participant’s legal rights, or releases or appears to release the investigator, the sponsor, the University, or its agents from liability for negligence.
Consent Documents for FDA Submissions

An investigational New Drug Application (IND) is not required to contain a copy of the consent document. If the sponsor submits a copy, or if FDA requests a copy, the Agency will review the document and may comment on the document’s adequacy.

For significant risk medical devices, the consent document is considered to be a part of the investigational plan in the Application for an Investigational Device Exemption (IDE). FDA always reviews these consent documents. The Agency’s review is generally limited to ensuring the presence of the required elements of informed consent and the absence of exculpatory language. Any substantive changes to the document made by an IRB must be submitted to FDA for review and approval.

Revision of Consent Documents during a study

Under certain circumstances subjects have to be re-consented. Examples include:

- Study participation is ongoing and
  - Subject reaches age 18
  - Subject regains competency
- New study information
  - Substantial Amendments to Protocol
  - Changes in study procedures
  - Changes in risk
  - Changes in subject payment
- New treatment became available

When these changes require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version. Documentation of re-consent should be provided.
Readability of Informed Consent

**Basic Principles of Readability:**

- Write at 8th grade level or below
- Use common, everyday words
- Define complex words using “Alternative word suggestions” or Glossary of Human Subject Terminology: http://research.ucdavis.edu/gt/g
- Use short sentences < 15 words
- Use active language/verb tense
- Use formatting (Bullets, white spaces, shaded boxes) to improve the visual understanding.
- Use visual aids, examples, analogs

**Non-English Speaking Subjects**

In the case of a non-English speaking subject, the FDA fully expects that a translated version of the ICF will be provided to the study subject. IRB assures that translation of the ICF is accurate.

A person who reads and speaks this language should administer the consent. Alternatively, a translator could be called in; however, while a translator may be helpful in facilitating conversation with a non-English speaking subject, routine ad hoc translation of the consent document should not be substituted for a written translation.

If a non-English speaking subject is unexpectedly encountered, and investigators do not have a written translation of the consent document, the investigators must rely on oral translation. Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented, the subject’s consent will not truly be informed and may not be legally effective. If investigators enroll subjects without an IRB approved written translation, a “short form” written consent document, in a language the subject understands, should be used to document that the elements of informed consent required by 21 CFR 50.25 were presented orally. Documentation of a short form is described in 21 CFR 50.27(b)(2). Briefly, when a short form consent document is to be used, the IRB should review and approve the written summary of the full information to be presented orally to the subjects. A witness is required to attest to the adequacy of the consent process and to the subject’s voluntary consent. Therefore, the witness must be present during the entire consent interview, not just for signing the documents. The subject or the subject’s legally authorized representative must sign and date the short form. The witness must sign both the short form and a copy of the summary, and the person actually obtaining the consent must sign a copy of the summary. The subject or the representative must be given a copy of the summary as well as a copy of the short form.
Iliterate English-Speaking Subjects

A person who speaks and understands English, but does not read and write, can be enrolled in a study by “making their mark” on the consent document, when consistent with applicable state law.

Physical disabilities preventing reading or writing

A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. The subject may be entered into the study if:

1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent), and
2) is able to indicate approval or disapproval to study entry.

The consent form should document the method used for communication with such subject and the specific means by which the subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document. A video tape recording of the consent interview is recommended.

Vulnerable Populations

The federal regulations require that IRBs give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. For research to which the HHS regulations are applicable, the HHS regulations set forth specific provisions on research involving fetuses, pregnant women, and human in vitro fertilization [45 CFR 46 Subpart B]

prisoners [45 CFR 46 Subpart C]; and children [45 CFR 46 Subpart D]. In general, these special regulations allow IRBs to approve research that is of minimal risk or that will benefit the subjects directly. Investigations involving these subjects that present significantly greater than minimal risk without direct benefit to them must be reviewed and approved by the Secretary of Health and Human Services, in consultation with appropriate experts.

Special considerations and procedures are required to be employed when obtaining consent from a legally authorized representative. Prior to engaging in any research that may involve obtaining surrogate consent, please refer to the IRB SOP #22 “Surrogate Consent for Research” to determine which individuals may serve as legally authorized representatives.
Consent and Assent of children

Where the research subject is a minor, special attention should be given to the informed consent process, because, as a general rule, minors lack the legal capacity to consent to the treatments or procedures involved in the research.

State laws define the age at which approval of older children are also required. Therefore, for research with children two documents are developed:

- For obtaining the parents’ permission (consent)
- For obtaining permission of children who can understand the concepts involved (assent).

The HHS regulations for conduct of studies in children may be used as guidance [45 CFR 46, Subpart D].

Parental consent. For subjects who are children, their parents or guardians (according to the definition of “guardian” in HHS and FDA regulations) are the legally authorized representatives who may grant permission for their participation in research. In such instances, satisfactory evidence of the person’s authority to consent on behalf of a child to general medical care is required and a determination is required to be made as to the scope of the authority under applicable state or local law. Grandparents and other relatives or caregivers may not grant permission unless they have been authorized under applicable state or local law (e.g. by a court) to consent on behalf of a child (i.e., whether the individual meets the HHS and FDA definition of a “guardian”). When enrolling a child into research using the permission of someone other than the child’s parent, the Principal Investigator (PI) is required to obtain a copy of the court order or other evidence of that person’s authority to grant permission for participation in research on the child’s behalf.

Minor’s legal status. There may also be special situations where a minor does not meet the HHS and FDA definition of “child.” This may be because of the minor’s status (e.g., emancipated minors and self-sufficient minors), or the nature of the procedures (e.g., pregnancy care, mental health treatment, drug or alcohol treatment). In such instances, satisfactory evidence of the minor’s legal status is required to be documented and a determination made as to the scope of the participant’s legal capacity to consent to the treatments or procedures involved in the research under the laws of the jurisdiction in which the research is conducted.

Wards of the State. A child who is a ward of the state or any other entity may be included in research involving greater than minimal risk that is not expected to directly benefit the child, if the research is:

1) Related to the child’s status as a ward; or

2) Conducted in schools, camps, hospitals, institutions or similar settings in which the majority of the subjects are not wards. Also, an advocate is required to be appointed by the IRB to act on behalf of the ward (or more than one ward) in addition to the child’s guardian. The advocate (a) is required to be qualified to act in each child’s best interests, and (b) may not be associated with the research, the investigator, or the guardian organization.
Minors in Custody of Foster Parents. Generally, licensed foster care providers may consent only to ‘ordinary’ medical and dental treatment (e.g., immunizations, physical examinations, x-rays). Written evidence of the foster parent’s authority to consent to enroll the minor in research is required and placed in the child’s medical and research records prior to proceeding.

Self-Sufficient or Emancipated Minors. A ‘self-sufficient minor’ is a minor who is 15 years of age or over, not living at home and manages his or her own financial affairs (California Family Code Section 6925). Self-sufficient minors may be enrolled only after consultation with the local IRB. The IRB (and, when necessary, legal counsel), will determine whether the self-sufficient minor has attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted.

An ‘emancipated minor’ is a minor 14 years of age or older who has been provided emancipation status by the State of California. The requirements are that the minor is at least 14 years of age and willingly lives separate and apart from the minor’s parents or guardian with the consent or acquiescence of the minor’s parents or guardian and the minor is managing his or her own financial affairs. As evidence of this process, under California law, the minor is required to complete and attach a declaration of income and expenses as provided in Judicial Council form FL-150. If the petition is sustained, the Department of Motor Vehicles will issue an identification card that states the minor is emancipated (California Family Code Section 7120). The investigator is required to obtain a copy of the minor’s identification card and place the copy in the subject’s medical record as well as the subject’s research records. California Family Code Section 7050 provides that “an emancipated minor may consent to his or her own medical, dental, or psychiatric care without parental consent, knowledge, or liability.” Therefore, an emancipated minor does not meet the HHS and FDA definitions of a “child,” and protections afforded a “child” are not applicable to emancipated minors.

Financial responsibilities of subjects

Financial responsibilities of the subjects should be clearly explained in the consent documents. Generally, there are three options.

1) the study is fully paid for by the sponsor, and no billing to the patient insurance occurs;
2) the study is fully paid for by insurance and no billing to the study occurs;
3) some study costs are billed to the insurance and some are covered by the study sponsor. This delineation should be reflected in the consent documents.

The consent should also clearly explain that subjects are still responsible for co-pays and deductibles based on their insurance coverage. Self-pay patients will be responsible for the costs of all services and procedures, unless the sponsor pays for all services/procedures for all participants on the study. The sponsor cannot be billed for the costs already billed to the third party, unless the patient qualifies for assistance under UCDHS’ charity care policy (UCDHS P&P 1891)³.

³ http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml
Subject Compensation for Participation

It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic, or device development. Payment to research subjects for participation in studies is not considered a benefit; it is compensation for their time and effort for participation. Financial incentives are often used when health benefits to subjects are remote or non-existent, such as in cases when healthy subjects are recruited. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither is coercive or present undue influence [21 CFR 50.20]. It is not advisable to pay a financial incentive to a subject when the patient is seen for research related services and insurance is going to be billed.

Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Subject injury

Since 1978, both HHS and FDA have required an additional element of consent regarding treatment and compensation for injury resulting from participation from research.

The current regulations for consent forms for research involving more than minimal risk indicate that the following must be included:

- An explanation as to whether any compensation and whether any medical treatments are available if injury occurs and,
- If so, what they consist of, or where further information may be obtained
While clinical sites typically provide medical treatment to the subjects sustaining injury/complication on the study, who will cover the costs may not always be a clear decision. Industry sponsor, insurance or even self-pay options may be considered. For privately sponsored studies (industry), the sponsor of the study is required to pay for injuries/complications directly resulting from the study material or research procedures performed in connection with the study protocol, granted that the injuries/complications were not a result of negligence, willful misconduct or failure to reasonably act on the part of the study personnel. The treatment of complications that are typical for this type of disease may be billed to the insurance. When the trial is sponsored by a Government Agency, the costs of treating study subjects for injuries/complications directly resulting from a study material or research procedures cannot be billed to that Agency. In these cases, the UC Human Subject Injury Program may cover these costs.

**Documentation of Informed Consent**

A signed and dated consent form is not sufficient in documenting the informed consent process. A written note (i.e. progress report, clinic note, etc.) should be created at each encounter documenting the communication between investigator and subject about the research. This note should include what was discussed; the fact that the subject’s questions were answered, if the subject received a copy of the consent form to take home, or if the subject signed the consent form. The accumulation of these notes over a period of time will document the consenting process.

In addition to signing the consent, the subject/representative should enter the date of signature on the consent document, to permit verification that consent was actually obtained before the subject began participation in the study. If consent is obtained the same day that the subject’s involvement in the study begins, the subject’s medical records/case report form should document that consent was obtained prior to participation in the research. A copy of the consent document must be provided to the subject and the original signed consent document should be retained in the study records.

The Federal Regulations don’t specify that it has to be a copy of the signed and dated consent form (DHHS 45 CFR 46.117(a) – Informed Consent) “...informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject’s legally authorized representative. A copy shall be given to the person signing the form.” However, the ICH GCP Guidelines (E6 4.8.11) and UCD IRB SOP#19, Informed Consent, do require that it does have to be a copy of the signed and dated consent form.
Waiver of the documentation of the Informed Consent

In limited circumstances, the IRB can waive the requirement for the investigator to obtain a signed consent form for some or all research participants.

A. Risk of Breach of Confidentiality [45 CFR 46.117 (c) (1)]

The IRB can waive the requirement for written documentation of informed consent for non-exempt research if all of the following criteria are met:

- The only record linking the participant and the research would be the consent document;
- The principal risk would be potential harm resulting from a breach of confidentiality;
- Each participant will be asked whether the participant wants documentation linking the participant with the research, and the participant’s wishes will govern;
- The research is not FDA-regulated.

B. Minimal Risk Research [45 CFR 46.117 (c) (2)]

The IRB can waive the requirement for written documentation of informed consent for non-exempt research if both of the following criteria are met:

- The research presents no more than minimal risk of harm to participants;
- The research involves no procedures for which written consent is normally required outside of the research context.

C. Additional Requirements

1. When the requirement for written documentation of consent is waived, the IRB must review a written description of the information (i.e., a “script”) that will be provided to participants (e.g., when consent is obtained by telephone or online). This information must include the basic elements of informed consent and any applicable additional elements as described above unless an alteration of consent has also been approved by the IRB.

2. When the requirement for written documentation of consent is waived, the IRB may also require that an investigator provide participants with a written statement regarding the research. Examples include approved consent forms (without signature lines), cards containing researcher and/or third party contact information, and information sheets outlining study procedures.
Use of Facsimile or Mail to Document Informed Consent

The IRB may approve a process that allows the informed consent document to be delivered by mail or facsimile to the potential participant or the potential participant’s legally authorized representative and to conduct the consent interview by telephone when the participant or the legally authorized representative can read the consent document as it is discussed with the person obtaining consent. All other applicable conditions for documentation of informed consent must also be met when using this procedure.

Deception Studies

As a general rule, deception is not acceptable when doing research with humans. Deception is the intentional misleading of subjects or the withholding of full information about the nature of the experiment. Misleading or omitted information might include the purpose of the research, the role of the researcher, or what procedures in the study are actually experimental. Deception increases ethical concerns, because it interferes with the ability of the subject to give informed consent. However, deception is arguably necessary for certain types of behavioral research. Because humans act differently depending on circumstances, full knowledge by the subject might bias the results. For example, in order to learn about decision-making practices of physicians without influencing their practice-style, they may be told that the research study involves “communication behaviors” in a broad sense. Federal regulations permit but establish limitations on the use of deception. The IRB will review any proposal that suggests using deception or misrepresentation very carefully. The IRB will require an in-depth justification of why the deception is necessary for the study and the steps the investigator will take to safeguard the participants.

The investigator should be able to demonstrate that:

- Deception is necessary to conduct the study;
- The subjects will be debriefed after the experiment is completed;
- The subjects will not be exposed to more than minimal risk; and
- The withheld information is not likely to change people’s decisions to participate in the study.

California Subject Bill of Rights

See page 64 and Appendix 3

References

Title 45 CFR (http://ohsr.od.nih.gov/guidelines/45cfr46.html#)
Title 21 CFR (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm)
California Family Code 6925 (http://law.onecle.com/california/family/6925.html)
California Family Code 7120 (http://law.onecle.com/california/family/7120.html)
CHAPTER 3: Regulations Affecting Clinical Research: Food and Drug Administration

Drug Development Process

Adapted from www.fda.gov/drugs

FDA’s Center for Drug Evaluation and Research (CDER) is responsible for regulating manufacturing, testing and importation of pharmaceutical drugs in the US. This includes new drug approvals, abbreviated new drug approvals (generics), over-the-counter drugs, animal drugs and biologics.

What is a drug?

Definition of “drug” includes articles (other than food):

- Intended for use in diagnosis, cure and mitigation of the disease
- Intended to affect the structure or any function of the body
- Intended to be used as a component of any of the above

Preclinical Testing

Preclinical testing involves lab and animal studies that evaluate the drug’s toxic and pharmacologic effects. Preclinical studies are also subject to the FDA regulations known as Good Laboratory Practices (GLP). The GLP regulations specify minimum standards in such areas as personnel, facilities, equipment and operations. Pre-clinical studies not performed under GLP conditions may not be accepted by the FDA. Recognition of this fact is particularly important for academic drug development.

Lasting 3-6 years, preclinical testing includes pharmacokinetics, the study of how the drug moves through living organisms. Researchers examine absorption, distribution, metabolism and excretion (also abbreviated as ADME) to ensure that the drug reaches its intended target and passes through the body properly. In addition to the biological tests, researchers conduct chemistry tests to establish the drug’s purity, stability and shelf life. Manufacturing tests are conducted to determine the feasibility of producing the drug on a large scale. Finally, pharmaceutical development studies are conducted to explore dosing, packaging and formulation (e.g., pill, inhaler, injection).

At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors: (1) develop a pharmacological profile of the drug; (2) determine the acute toxicity of the
drug in at least two species of animals, and (3) conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products.

Investigational New Drug (IND) Application (21 CFR Part 312)

After preclinical testing is completed, a company or academic sponsor-investigator (see below) files an IND with the U.S. Food and Drug Administration (FDA) prior to beginning any human testing. An IND is a request for the FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any unapproved drug.

The application must show results of preclinical experiments; the chemical structure of the compound; how it is thought to work in the body; any side effects found in animal studies; and how the compound is manufactured (chemistry, manufacturing and controls section). The IND must also include a detailed clinical trial plan, including how, where, and by whom the studies will be conducted.

Based on the information of the IND application, the FDA will determine if there is sufficient evidence to support initial human testing. The sponsor must wait 30 days after submitting the IND to the FDA for review. At the end of the 30 day review period, unless the FDA identifies a potential safety problem involving the use of the drug and asks for a delay, the sponsor may begin the proposed clinical testing.

Is an IND required for studies with drugs already approved by the FDA

Many clinical studies by academic investigators involve marketed drugs, often to establish efficacy in a new indication. Studies with lawfully marketed drugs require IND submissions, unless these studies comply with six exemption criteria laid out in 21 CFR 312.2. One of the exemption criteria should be considered very carefully when deciding whether the study is exempt:

The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product.


Thorough documentation is required to support the exemption criteria and may include prior publications or other public disclosures. If such evidence cannot be provided, a physician should submit a research IND (limited in scope) to the FDA. The physician is now considered a sponsor-investigator.

Is an IND required for studies with dietary supplements?

Many clinical studies of academic investigators evaluate the effect of dietary supplements on the disease or physiological parameters. Some of these studies may require an IND submission. If the dietary supplements are investigated for diagnosis, cure, mitigation, treatment, or prevention of disease and are used to affect the structure or function of the body, then the dietary supplement will be considered a drug and require an IND, reviewed by a division at CDER pertinent to the disease indication. Proposals for studying extracts from plants may be classified as “botanical drug” products, and will be reviewed by the FDA Botanical Review Team. Unique characteristics of botanical drugs include:

- Derivatives from plants, algae, macroscopic fungi and combinations of these
- Complex mixtures
- Chemical constituents not well defined
- Active constituent(s) may not be identified
- Biological activity not well characterized
- May have been used previously by large numbers of people

The study will be the subject to the same regulations as any other unapproved drug. IND submissions for “botanical drugs” are markedly reduced in scope. An investigator should seek a consultation with the Botanical Review Team prior to IND submission.

Expanded Access of Investigational Drugs:

**Treatment IND (21 CFR 312.320)**

A treatment IND allows patients whose needs for treatment outweigh the risks (e.g. life-threatening illness) to obtain access to investigational treatment prior to completion of pivotal clinical trials. The FDA will allow an investigational drug to be used under the Treatment IND if there is preliminary evidence of drug efficacy, which means that Phase III clinical trials with this drug must be well underway. Typically, such patients are not eligible for the on-going trials and no alternative therapy is available. Such INDs require IRB review and Informed consent. The list of approved Treatment INDs is posted on the FDA website.
Expanded Access of Investigational Drugs: Group C Treatment IND

Group C drugs are Phase III cancer drugs that have shown evidence of reproducible efficacy. These drugs are distributed by the NIH under NCI protocols. Treatment is a primary objective, but safety and effectiveness data are still collected. FDA generally grants the waver from the IRB review requirements.

Expanded Access of Investigational Drugs: Single-patient INDs (Emergency Use and Non-Emergency Use)

The need for investigational drug may arise in an emergency situation that does not allow for IND submission and IRB review. A physician who wishes to administer an investigational drug under the Expanded Access: Single-Patient program is responsible for procuring the drug from the sponsor, securing IRB approval and providing informed consent consistent with standard FDA rules (subject to emergency use exceptions provided in those rules), reporting adverse drug events to the sponsor, and maintaining accurate drug accountability and patient case history records. A physician who is unable or unwilling to meet these demands should not proceed. For detailed description of how a single-patient IND is executed at UC Davis, see UC Davis Policy and Procedure P&P15099.

Form 1571 (Investigational New Drug Application)

All IND submissions (initial and all subsequent) should be accompanied by a Form 1571. Please note “OMB No.” in the upper right corner of the Form. While at the date of the printing of this manual the expiration date is May 31, 2009, it is important to check for the newest versions of this form. The most recent version of the 1571 is available online.

Detailed guidance on how to fill out the Form 1571 is also available online.

Form 1572 (Statement of Investigator)

The Statement of Investigator, Form FDA 1572, is an agreement signed by the investigator to assure that he/she will comply with FDA regulations related to the conduct of a clinical investigational drug or biologics. The investigator’s signature on this form constitutes the investigator’s affirmation that he or she is qualified to conduct the clinical investigation and constitutes the investigator’s written commitment to abide by FDA regulations in the conduct of the clinical investigation. The most recent version of the 1572 is available online.

Detailed guidance on how to fill out Form 1572 is also available online.

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6 http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml
7 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf
8 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm#form1571
9 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf
Form 3674 (Certification of Compliance)

Title VIII of FDAAA, Public Law 110-85, amended the PHS Act by adding new section 402(j), 42 U.S.C. § 282(j). The new provisions require that additional information be submitted to the clinical trials data bank (www.ClinicalTrials.gov) previously established by the National Institutes of Health (NIH)/National Library of Medicine (NLM), including expanded information on clinical trials and information regarding the results of clinical trials. The statutory requirement to submit a certification (FDA Form 3674) applies among other things to Investigational New Drug Applications (INDs) and the submissions of new protocols to INDs. Typically, for new investigator-initiated INDs, box C is marked, which means that the trial will need to be registered with clinicaltrials.gov. Single patient, emergency use INDs do not fall under the referenced section and therefore are not required to submit certification.

Phases of Clinical Trials

Phase I Study

The first of four phases of clinical trials, Phase I studies are designed to establish the effects of a new drug in humans. These studies are usually conducted on small populations of healthy humans to specifically determine a drug’s toxicity [or maximally tolerated dose (MTD)], absorption, distribution and metabolism. Phase I studies may also enroll subjects with the targeted disease who have already tried and failed to improve on the existing standard interventions. A typical sample size is 20-80 individuals. The information obtained in this phase permits the design of well-controlled, scientifically valid Phase II studies.

Phase II Study

After the successful completion of phase I trials, a drug is then tested for safety and efficacy in a slightly larger population of individuals who are afflicted with the disease or condition for which the drug was developed. Phase II includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase II studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.

Phase III Study

The third and last pre-approval round of testing of a drug is conducted on large populations [several hundred to several thousand] of afflicted patients. Phase III studies usually test the new drug in comparison with the standard therapy. The results of these trials usually provide the information that is included in the package insert and labeling.
Phase IV Study

After a drug has been approved by the FDA, phase IV studies may be conducted to compare the drug to a competitor, explore additional patient populations, or to further study any adverse events. Phase IV or “post-marketing” studies may also evaluate long-term safety or generate more data about how the medicine affects a particular group of patients (e.g., children or the elderly). Depending on the findings, a company can use the studies to submit a Supplemental NDA, seeking additional indications for the drug.

Device Development Process

FDA’s Center for Devices and Radiological Health (CDRH) is responsible for regulating manufacturing and importation of medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions.

Is my device a medical device?

If a product is labeled, promoted or used in a manner that meets the following definition in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act it will be regulated as a medical device. A device is:

“an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

This definition provides a clear distinction between a medical device and other FDA regulated products such as drugs. If the primary intended use of the product is achieved through chemical action or by being metabolized by the body, the product is usually a drug. In cases where it is not clear whether a product is a medical device, a Device Determination Officer can assist in making a determination.
Device Classification

The FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes (Class I, II and III) based on the level of control necessary to assure the safety and effectiveness of the device. The device classification defines the regulatory requirements for an approval of a new device. Regulatory control increases from Class I to III.

Device classification depends on the intended use of the device and also upon indications for use. In addition, classification is based upon the risk the device poses to the patient and/or the user. Examples:

- **Class I devices**: elastic bandages, examination gloves, and hand-held surgical instruments.
- **Class II devices**: powered wheelchairs, infusion pumps, and surgical drapes.
- **Class III devices**: implantable pacemaker pulse generators and coronary stents.

To find the classification of your device, as well as whether any exemptions may exist, you need to find the regulation number that is the classification regulation for your device. One of the ways to accomplish this is to go directly to the classification database and search for a part of the device name.

Once you have identified the correct classification regulation go to the device panel (medical specialty) to which the device belongs.

The search will provide you with the Device Classification and the appropriate regulation. If the device is not classified, you can research similar devices on the FDA website (PMA and 510(k) databases) or use pre-IDE consultation for the FDA determination.

**PMA vs 510(k)**

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III (and some Class II) medical devices. Due to the level of risk associated with certain devices, FDA needs to see sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). The content of PMA is similar to the NDA for new drugs, and contains manufacturing sections, pre-clinical laboratory studies and clinical investigations.

Some devices (from Class I or Class II) may be able to be approved under a different pathway colloquially called 510(k). The name refers to requirements outlined in section 510(k) of Food, Drug and Cosmetics Act. If the device is considered substantially equivalent to one or more similarly marketed devices (known as “predicate” devices), a claim of substantial equivalence can be made. A claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design and other parameters.

**Significant Risk vs Non-significant Risk**

Devices used on human subjects to conduct investigations of safety and effectiveness are considered “Investigational Devices” (Section 520(g) of FDCA).

**Significant Risk (SR) device** presents a potential for *serious risk of health, safety and welfare of a subject,* and:

- Intended to be used as an implant and;
- Purported to support or sustain human life;
- Is used for substantial importance in diagnosing, curing, mitigating or treating disease

Examples of SR devices include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants. Conversely, **non-significant risk (NSR) device** study does
not pose a significant risk to patients. Non-significant risk should not be confused with “minimal risk,” a term used by the FDA to classify studies. Examples of NSR devices include most daily-wear contact lenses and lens solutions, ultrasonic dental scalers, and foley catheters.

SR devices must meet all regulatory requirements set in 21 CFR 812, including the requirement for approval by both IRB and the FDA before commencing the study. An investigational device exemption (IDE) is a regulatory submission to the CDRH. If approved, it allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data.

NSR device studies may commence without FDA approval, based solely on the IRB approval. However, the sponsor-investigator must follow abbreviated IDE requirements, which are, in essence, the same requirements as regular IDE only without FDA submission (21 CFR 812.2 (b)). The IRB acts as a surrogate overseer for the FDA.

For comparison of full and abbreviated IDEs, see Appendix 6

FDA guidance document Significant Risk and Non-significant Risk Medical Device Studies can be used to help classify a device12.

Investigational Device Exemption (IDE)

An IDE is required when a significant risk study is testing an FDA-approved device for a new indication.

IDE requirements:

• Study approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA;
• informed consent from all patients obtained and documented;
• the device is labeled “CAUTION- Investigational Device. Limited to investigational use only;”
• Sponsor-investigator complies with monitoring requirements;
• Records and reports are maintained;
• Investigator cannot promote or commercialize (charge for) the device.

Some studies may be exempt from the IDE regulations (21 CFR 812.2(c)):

1) a legally marketed device when used in accordance with its labeling,

2) a diagnostic device if it is:
   - noninvasive;
   - does not require an invasive sampling procedure that presents significant risk;
   - does not by design or intention introduce energy into a subject;
   - and is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure;

3) consumer preference testing…of legally marketed device(s)

4) a device intended solely for veterinary use;

5) a device shipped solely for research with laboratory animals

**Humanitarian Use**

HUD (Humanitarian Use Device) designation requests are the first step in seeking marketing approval of a HUD. The second step is a submission of a Humanitarian Device Exemption (HDE) application to the Center for Devices and Radiological Health (CDRH).

HUD is a “medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.” (21 CFR 814.39(n)). The request for HUD designation is described in the FDA Guidance “Designating Humanitarian Use Devices”\(^\text{13}\).

If the request is granted, the investigator proceeds with the submission of HDE. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

\(^{13}\) http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/DesignatingHumanitarianUseDevicesHUDs/LegislationRelatingtoHUDsHDEs/ucm283517.htm.
Emergency Use of Unapproved Device

An unapproved medical device is a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval (510(k)) or an approved IDE. Emergency use is permitted if the treating physician determines that:

- The patient has life-threatening condition that needs immediate treatment
- No generally acceptable alternative treatments exist
- Because of an immediate need there is no time to use existing procedures for CDRH approval

Next, the treating physician needs to undertake the following protective measures:

- An independent assessment by an uninvolved physician
- Informed consent from the patient or legal representative
- Approval of the IRB Chair
- Approval from the IDE sponsor, if any
- Prior FDA approval for shipment or emergency use of the investigational device is not required, but the use should be reported to the FDA by the IDE sponsor via a supplement within 5 working days from the time the sponsor learns of the use

Note that if a physician, who is faced with an emergency situation contacts the FDA to discuss his/her patient’s condition, the FDA will only act in an advisory role, rather than in an approving role. **The responsibility for making the decision as to whether the situation meets the emergency use criteria and whether the unapproved device should be used lies with the physician.**

For guidance on reporting emergency use to the FDA, see CDRH Guidance for the emergency use of unapproved medical devices ([http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm)).

For implementation of the Federal Guidelines at UC Davis, see the UCDHS Policy and Procedure P&P151014.

Compassionate Use of Investigational Devices

This type of use is NOT an emergency use. A request to use an investigational device in the mitigation, diagnosis and treatment of serious diseases requires an IDE Supplement (see below). The sponsor or investigator has to submit the protocol for

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use of the device in a single patient or a group of patients. In order to permit this use, CDRH will review the following information:

- No comparable alternative treatment exists
- Sufficient evidence of safety
- Clinical use will not interfere with ongoing clinical investigations

Treatment Use

This type of use is NOT an emergency use. A request to use an investigational device in the mitigation, diagnosis and treatment of serious diseases requires a Treatment IDE Submission. If approved, treatment IDE enables a wider group of patients to receive the investigational device for the same indication as it is being studied under the sponsor IDE. Treatment IDE will remain open even after the sponsor trial has been completed. The following provision have to be met:

- Device is investigated in a controlled clinical trial under IDE for the same use
- Sponsor is actively pursuing market approval
- No comparable alternative treatment exists
- Clinical use will not interfere with ongoing clinical investigations
- Sufficient evidence of safety and effectiveness

New Drug Application (NDA)

After clinical trials have been completed demonstrating safety and effectiveness, the drug sponsor will submit a New Drug Application (NDA) to the FDA for a license to market the drug for a specified indication. NDAs contain all of the information about all of the studies, including preclinical testing, all clinical trials, dosing information, manufacturing details and proposed labeling for the new medicine.

FDA Review/Approval

At this point, FDA scientists review all the results from all the studies carried out over the years and determine if they show that the medicine is safe and effective enough to be approved. During this review, the FDA determines what the labeling should be and whether the sponsor can manufacture it properly and consistently. Once the drug is approved, it becomes available for physicians to prescribe for the indication approved by the FDA. The review process takes approximately 18 months.
References

CDER (http://www.fda.gov/Drugs/default.htm)

Title 21 CFR (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm)

Group C Treatment IND (http://www.fda.gov/RegulatoryInformation/Guidances/ucm126495.htm)


CDRH (http://www.fda.gov/MedicalDevices/default.htm)

Premarket Approval (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm)

510k (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm#whennot)

IDE (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm)

Arbit, H.M. How to prepare an Investigational Device Exemption (IDE) as a Sponsor-Investigator. SoCRA Source, November 2009, p.58.


Medical Device Development: Regulation and Law. ©2009PAREXEL. Edited by: JonathanS.Kahan, Partner, Hogan& Hartson, LLP.
Chapter 4: Regulations Affecting Clinical Research: Center for Medicare Services

The Centers for Medicare Services (CMS) Medicare coverage rules for clinical research services are stated in the National Coverage Determination (NCD 310.1) Policy, most recently revised in July 2007. According to this policy, Medicare will reimburse for additional costs incurred by the participants in qualifying clinical trials. These additional (expanded) costs may include administration of the investigational item (e.g., chemotherapy infusion), clinically appropriate monitoring (e.g. additional labs to monitor for side effects of the investigational medication) and diagnosis, prevention and treatment of complications. In order to receive the reimbursement for expanded services, the study has to “qualify.” The NCD specifies the qualification process for clinical trials, including covered indications, limitations of coverage, and other requirements (See Chapter on Coverage Analysis). Medicare coverage for clinical trials is limited to items and services that are reasonable and necessary and within the scope of a Medicare benefit category. If services are only being obtained for data collection and not reasonable and necessary, the service is non-covered, and therefore, should be paid for by the study budget.

This NCD necessitates a priori delineation of what clinical trial services/procedures could be billed to Medicare, and which could only be billed to the study. Such delineation can be expressed in a Medicare Coverage Analysis (MCA) or simply Coverage Analysis (CA). At UC Davis, the Coverage Analysis is required for all clinical trials in which some tests, procedures and interventions performed on study subjects are invoiced to third party payers (See p. 69, Coverage Analysis).

CMS Medicare contracts with local intermediaries to administer the Medicare program. The local Medicare contractor (intermediary) for California is Palmetto GBA. At the local level, in the absence of a national coverage policy, each Medicare contractor has the discretion to determine which items and services are reasonable and necessary and therefore covered as a Medicare benefit. Some coverage determinations are issued in a document called a Local Coverage Determination. National Coverage Decisions always have higher importance than Local Coverage Decisions. The local contractor also determines approval for coverage when providers request recognition as participants in device trials. Providers must adhere to device coverage instructions in the CMS manual (Palmetto GBA)15. Specific claims processing instructions can be found in the Medicare Claims Processing Manual and in the NCD 310.1.

15 http://www.palmettogba.com/palmetto/providers.nsf/DocsCat/Providers~Jurisdiction%201%20Part%20A~Articles~Investigational%20Device%20Exemptions%20(IDEs)~7QUQER5058?open&navmenu=%7C%7C
For Medicare, the following resources are available as tools for determining coverage:

CMS Online NCD database (http://www.cms.gov/)

Palmetto (www.palmettogba.com)

CMS Regulations and Guidance Manuals\(^ {16} \ 17 \);

National Correct Coding Initiatives Edits\(^ {18} \);
CHAPTER 5: Navigating Clinical Research Administrative Process at UC Davis

Required Training

UC Davis conducts research studies according to FDA regulations and ICH guidelines. Standardized training and continuing skill development of all clinical research professionals is an important part of preparation for clinical research. It is the responsibility of all staff and investigators to know, understand and maintain sufficient knowledge of the federal, state and local requirements for protecting research participants. For details see CTSC Clinical Research SOP #19.

New Employee Requirements

In accordance with UCDHS policy, all new research staff will attend the “New Employee Orientation” and complete the mandatory annual training.

CITI

UC Davis employs the Collaborative Institutional Training Initiative (CITI) program – a web based training program to satisfy the training requirement for all personnel conducting human subjects research under the auspices of UC Davis. Certification is valid for 3 years. For more information, please see: http://research.ucdavis.edu/u/a/irb.

Dangerous Goods Shipping for Infectious Substance and Dry Ice

Research staff working with specimens must complete and be certified to process, transport, or ship specimens. The class covers shipment of Class 6.2 Infectious Substances and Diagnostic specimens and Class 9 Miscellaneous Substances (e.g. dry ice). Certification is valid for two years. Enroll on-line at http://lms.ucdavis.edu.

Lab Safety Training

Annual lab safety training is required for all research staff working with specimens. This training covers working with human blood, body fluids and unfixed tissue, which falls under the category of potential/known blood borne pathogens. The training covers specimen handling, biowaste disposal, lab accident and incident cleanup and reporting. For more details see http://www.ucdmc.ucdavis.edu/medresearch/medsp/labsafety.html.

Clinical Research Training Program

The Clinical and Transitional Science Center (CTSC) publishes a calendar of training events. The Clinical Trials Resource Group (CTRG) offers monthly training featuring seminars, workshops, SoCRA brown-bag meetings and a 2-day Clinical Research
Coordinator Training program. CTRG aims at improving clinical research process flow and operations. More information can be found at: http://www.ucdmc.ucdavis.edu/ctsc.

New Submitter Training

New Submitter’s Training is conducted quarterly by the IRB. This orientation provides detailed training on the ethical principles of human subjects research, an explanation of the researcher’s primary responsibility for protecting research subjects and for complying with all applicable provisions of the institution and state and federal laws. It provides explanation of the different levels of IRB review from submission process and approval through the annual review and description on how to complete the IRB forms (IRB SOP #14, Education and Training requirements20).

Coverage Analysis and Budget Training

For in-service Coverage Analysis and Budget training please contact Suzan Bruce (916-703-0120) and Julie Calahan (916-734-2547).

UCDHS Mandatory Annual Training (http://www.ucdmc.ucdavis.edu/cppn/mat/)

This is the annual safety training and code of conduct required for all UC Davis Health System employees as required by The Joint Commission, State of California, Department of Public Health and UC Davis Health System Hospital Policy 2903.

UCDHS Privacy and Security Training (http://www.ucdmc.ucdavis.edu/compliance/Quiz/PrivacySecurity/player.html)

The objectives of the training is to understand what information must be protected under State and Federal privacy laws, what rights patients have regarding access and use of their medical information. It also addresses employee role in maintaining privacy and security of medical data and the consequences of non-compliance.

Preparatory Research

Research Preparation Application

On occasion researchers may need to look at Protected Health Information (PHI) for preliminary purposes such as evaluating feasibility of a research project, designing data collection forms, etc. In these cases, a researcher can apply for access to the PHI under the “review preparatory to research” portion of Health Insurance Portability and Accountability Act (HIPAA). A request must be sent to the privacy officer with:

1) A statement that the work is solely to review PHI to prepare a research protocol or for similar purposes preparatory to research
2) A statement that no PHI will be removed from the entity holding it
3) A list of the elements of PHI that are necessary for the work

20 http://research.ucdavis.edu/gt/d/irb/
Limited Data Sets

A limited data set is PHI that excludes certain identifiers but permits the use and disclosure of more identifiers than in a de-identified data set. In particular, the limited data set allows the inclusion of all dates, 5 digit ZIP codes, and city as indirect identifiers. A limited data set may be used only for the purposes of research, public health, or health care operations. UC Davis Health System may use or disclose limited data set information only if it enters into a valid data use agreement (http://www.ucdmc.ucdavis.edu/compliance/pdf/datuse.pdf).

De-identified datasets

Once protected health information (PHI) has been de-identified, it is no longer PHI, and the restrictions and requirements of federal and state privacy laws no longer apply. There are two methods of de-identification: 1) use of statistical methods proven to render information not individually identifiable, and 2) deletion of 18 specified identifiers. Follow these guidelines to de-identify datasets: http://www.ucdmc.ucdavis.edu/compliance/guidance/privacy/deident.html.

Cohort Discovery

Subject counts can be obtained using the Cohort Discovery Tool (http://www.ucdmc.ucdavis.edu/ctsc/area/informatics/cohortdiscovery/). Cohort Discovery is a repository of de-identified patient information gathered from multiple sources, including UCDHS electronic medical records and billing records. This information is de-identified using recognized best practices as described above. A user interface known as the query workbench allows researchers to create queries, based on disease diagnosis code, age, sex, lab results and a few other values. Once the cohort is found, the researcher may ask the IRB for approval to request PHI data based on this cohort for recruitment purposes. The CTSC Biomedical Informatics team provides data extraction.
REDCap

UC Davis adopted the Research Electronic Data Capture system (REDCap) as a secure software application for building and managing online clinical research databases. The application allows users to create research databases and data entry web-based screens and link data collected with existing statistical software tools. It is a replacement for all Microsoft Excel spreadsheets and Access databases for study data, improving data security, online access, and the quality of data collected.

What does REDCap support?

- Rapid creation and design of projects by construction a “data dictionary” template file in Microsoft Excel, for upload into REDCap for execution
- Built-in project calendar and scheduling capabilities
- Audit trails for tracking data manipulation and user activity
- Automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages (SPSS, SAS, Stata, R)

Learn more about REDCap Data Management Software at: http://www.ucdmc.ucdavis.edu/ctsc/redcap/.

Roles and responsibilities of the PI and Research staff

Principal Investigator (PI)

An Investigator is an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. “Sub-investigator” includes any other individual member of that team (21 CFR 321.3 (b)).

An investigator’s responsibilities in conducting clinical investigations of drugs or biologics are provided in 21 CFR Part 312. Many of these responsibilities are included in the Form FDA 1572, which is an agreement between investigator and the sponsor or between investigator and the FDA (if the investigator is a sponsor-investigator).

An investigator’s responsibilities in conducting clinical investigations of a medical device are provided in 21 CFR Part 812. The investigator signs an agreement with the sponsor or with the FDA (if the investigator is a sponsor-investigator) which is included in the IDE application.
Academic investigators tend to equate the term “Sponsor” with a source of the study funding. In fact, there are two types of sponsors: regulatory sponsor and financial sponsor. The regulatory sponsor is the person/entity who initiates and takes responsibility for a clinical investigation. The regulatory sponsor submits the IND (or IDE) and is responsible for communications with the FDA. The regulatory sponsor may be a pharmaceutical company, a private or academic organization, or an individual. If an academic investigator authored the study protocol, is a principal investigator and oversees the study, the investigator is the regulatory sponsor (aka sponsor-investigator) and he/she carries all burden of regulatory compliance.

A Sponsor-Investigator is an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is being administered or dispensed. A sponsor-investigator has the obligations of both the investigator and the sponsor (21 CFR 813.3(o))

A financial sponsor may be a company, a department, a non-profit or a governmental agency. If a pharmaceutical company is supplying a drug for an academic study, but will not be submitting the IND, the company is not the regulatory sponsor. For commercial INDs, the financial and regulatory sponsor are usually the same (drug company).

Investigator and Sponsor-Investigator responsibilities are outlined in multiple regulatory documents, including 21 CFR 312.60, the FDA Guidance on Investigator Responsibilities, IRB SOPs #47 and #48, and ICH E6 (GCP) – Section 4.

Below is the brief summary of the responsibilities and available resources:

1) Ensures that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations (ICH E6 4.5).

2) Abides by commitments agreed to in Section 9 of the 1572:
   • Strict adherence to the study protocol (for example, inclusion/exclusion criteria, schedule of events etc)
   • Knowledge of and adherence to the regulations governing conduct of clinical investigations

3) Qualified by education, training and experience (ICH E6 4.1). The IRB Committee is required to ensure that all Investigators are competent and licensed, if applicable, relevant to the scope and complexity of the research

21 http://research.ucdavis.edu/gt/d/irb/
conducted. The IRB Committee may request additional information, qualification documentation, or licensure to assure competence in performing proposed research activities (IRB SOP #48).

4) Protects the rights, safety, and welfare of subjects under the investigator’s care by:

• Submission of all study subject related materials to the IRB and maintain IRB approval throughout the term of the study (ICH E6 4.4)

• A thorough discussion of the study with potential study subjects, obtaining and documentation of the Informed Consent for participation (ICH E6 4.8)

• Performing all study protocol safety procedures according to prescribed study protocol schedule

• Monitoring for and reporting of any Adverse Events or Serious Adverse Events to the IRB, FDA and to the study sponsor

5) Assures documentation of study-related procedures, processes and events (ICH E6 4.9):

• Regularly reviewing his or her research processes and address any deficiencies identified, documenting of audits of his/hers research activities and external sites on a regular basis (IRB SOP #47).

6) Being available to provide and providing reasonable medical care to subjects for any adverse events related to study participation (ICH E6 4.3).

7) Maintaining control of drugs under investigation (ICH E6 4.6):

• Maintain accurate and up to date drug accountability records

• Ensuring secure and proper storage and dispensing procedures for all investigational drugs

8) Assures the validity of the data reported to the sponsor (or FDA) (ICH E6 4.9).

9) Determines that adequate resources are available to conduct the study (ICH E6 4.2). In the event the resources necessary to protect participants become unavailable during the course of the study, the Principal Investigator should stop the study until those resources are once again available (IRB SOP # 47).

10) Ensures participant privacy and confidentiality and data confidentiality according to HIPAA guidelines, Institutional and IRB policies and standard operating procedures (IRB SOP #47).
UC Davis School of Medicine Specific Requirements

According to UCDHS specific requirements, the PI is also ultimately responsible for financial performance of the trial, including:

- Disclosure of applicable conflicts of interest (COIs)
- Providing feasibility assessment
- Developing Coverage Analysis for Full Committee and Expedited studies
- Developing and negotiates study budgets
- Ensuring billing adjustments as required

See Chapter on Pre-Approval Financial Requirements for details.

Sponsor-Investigator Obligations

21 CFR part 50 details sponsor obligations. Sponsors are responsible for:

- selecting qualified investigators,
- providing them with the information they need to conduct an investigation properly,
- ensuring proper monitoring of the investigation(s),
- ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND,
- maintaining an effective IND with respect to the investigations,
- and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

Additional specific responsibilities of sponsors are described elsewhere in this part. For example,

§ 312.53 - Selecting investigators and monitors
§ 312.54 - Emergency research under 50.24 of this chapter
§ 312.55 - Informing investigators
§ 312.56 - Review of ongoing investigations
§ 312.57 - Recordkeeping and record retention
§ 312.58 - Inspection of sponsor’s records and reports
§ 312.59 - Disposition of unused supply of investigational drug
21 CFR part 60 details **investigator obligations**. Investigators are responsible for:

- ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations;
- for protecting the rights, safety, and welfare of subjects under the investigator’s care;
- and for the control of drugs under investigation.
- An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 50.23 or 50.24 of this chapter.

Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

§ 312.61 - Control of the investigational drug  
§ 312.62 - Investigator recordkeeping and record retention  
§ 312.64 - Investigator reports  
§ 312.66 - Assurance of IRB review  
§ 312.68 - Inspection of investigator’s records and reports  
§ 312.69 - Handling of controlled substances  
§ 312.70 - Disqualification of a clinical investigator

A helpful checklist of the FDA regulations along with the corresponding onsite documents can be found at [http://www.partners.org/phsqi/ToolsPage.htm](http://www.partners.org/phsqi/ToolsPage.htm)

**Delegation of Responsibilities by the Principal Investigator**

It is common practice for investigators to delegate certain study-related tasks to employees, colleagues, or other third parties (individuals or entities not under the direct supervision of the investigator). However, the Principal Investigator (PI) is **ultimately responsible** for the conduct of the study. When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. Investigator creates a delegation log, indicating delegated tasks and designated individuals. The same applies to staff/contract organizations not in direct employ of investigator.
Example:

<table>
<thead>
<tr>
<th>Title of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
</tr>
<tr>
<td>John Smith</td>
</tr>
</tbody>
</table>

The investigator has to assure that the staff has appropriate education, training and experience to perform delegated tasks. The training is documented in the training log. See Chapter on Required Training for more details.

Some staff performing phlebotomy (blood draws) may need to obtain phlebotomy certification from the California Department of Public Health:

http://www.cdph.ca.gov/programs/lfspages/Phlebotomist.aspx

Alternatively, a short course from a commercial certification program, such as Boston Reed College (http://www.bostonreedcollege.com/phlebotomy-technician.cfm) may be sufficient for research purposes.

Staff members performing EKG, vitals and simple diagnostic procedures (such as pregnancy test by urine dipstick) have to receive proficiency certification from CTSC Clinical Research Center.

The investigator should develop a plan for the supervision and oversight of the clinical trial at the site. Supervision and oversight should be provided even for individuals who are highly qualified and experienced. Such plan is outlined in the FDA Guidance on Investigator responsibilities and may include routine meetings, procedures for reviewing staff performance, procedures for correction of protocol deviations, procedures for ensuring quality control, and others.
Clinical Research Coordinator (CRC) or similar staff role

The primary responsibility of the research nurse/coordinator is to manage daily aspects of the conduct of the clinical trial. Collectively referred to as Clinical Research Coordinators (CRCs), the CRC is required to have in-depth knowledge of the protocol and GCP. The CRC responsibilities include, but are not limited to, the following:

- Assures protocol compliance through a thorough understanding of the protocol
- Assists with study start up
- Screens and enrolls study participants
- Tracks participant compliance with the research drug, device or procedure
- Completes source documents, if applicable, and case report forms (CRFs)
- Tracks, reports, and monitors adverse events
- Prepares regulatory documents as needed for the FDA (e.g., Form 1571, 1572) and Institutional Review Board (e.g. Description of Study, Informed Consent Form).
- Complies with sponsor and/or FDA audit requests
- Assists with study close out
- Trains and supervises other research support staff, as needed

UCDHS-specific Requirements:

- Prepares the Coverage Analysis under the PI supervision (if applicable)
- Prepares budgets under the PI supervision, and reconciles the monthly billing statements (if applicable)
- Works with financial analysts of the department to prepare accounts receivable entries based on the patient enrollment and progression though the clinical trial.
- Properly identifies study patients in the electronic medical records (EMR); creates research diagnosis codes with pertinent study information; associates orders with the research diagnosis code where appropriate, pends orders in EMR
CLINICAL AND TRANSLATIONAL SCIENCE CENTER

Clinical Trials Resource Group

The Clinical Trials Resource Group has undertaken the goal of transforming the clinical research enterprise into a more integrated structure. In addition to facilitating the compliance with the clinical trials regulations (including OHRP, FDA and Medicare), the group serves as a catalyst for reorganization of the institutional functions necessary for the next generation of clinical research. The group facilitates CRC and Department Managers workgroups aiming at improving clinical research process flow and operations. The group actively participates in National CTSA taskforces including Clinical Research Management and Regulatory Knowledge and Support.

Clinical Trials Resource Group provides:

1. Logistical support for clinical trials, including assistance with IRB documentation, IND/IDE submissions, Clinical Research Billing and temporary coordinator-for-hire
2. Education and training of investigators and staff
3. Clinical trials monitoring

To assist with Navigating clinical trials at UC Davis, the Clinical Trials Group maintains Clinical Trials Process Maps. The functional process maps reflect administrative infrastructure for clinical research, including budgeting and billing, regulatory compliance, electronic patient tracking etc. To help navigate operational activities, the maps are divided into specific tasks that must take place to ensure completion of each activity.

Many activities are linked with the appropriate SOPs, P&Ps, forms, contacts or websites. Using this map for navigation of administrative landscape will enable you to anticipate and plan your next steps.

Process maps and CTSC SOPs can be found at: http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml

CTSC Clinical Trials Resource Group
Clinical and Translational Sciences Center
2921 Stockton Blvd, Suite 1400
Sacramento CA 95817
www.ucdmc.ucdavis.edu/CTSC/area/clinicaltrials/
(916) 703-9177
Pre-Approval Regulatory Submissions

IRB Administration
Clinical and Translational Science Center (CTSC)
2921 Stockton Blvd., Suite 1400, Room 1429
Sacramento, CA 95817
http://www.research.ucdavis.edu/u/a/irb

UC Davis IRB Committees

The UC Davis IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research studies conducted under the auspices of the University of California, Davis. The role of the IRB is to review and to make decisions on all research involving human subjects at UC Davis. UC Davis has four IRB committees: two clinical, one social & behavioral and one central IRB (CIRB).

Committees “A” and “B”
Reviews research that is primarily biomedical or clinical in nature.

Committee “C”
Reviews any research that is primarily social or behavioral in nature.

Committee “D”
Reviews all cancer studies approved by a central IRB.

Criteria for IRB Approval

In order to evaluate and potentially approve human subjects research, the UC Davis IRB must review and determine that all of the federal requirements for approval, as outlined in 45 CFR 46.111(a)(1-7)(b), are satisfied (UC Davis IRB SOP #34-22):

- Risk to subjects is minimized
- Risks to subjects are reasonable in relation to anticipated benefits
- Selection of subjects is equitable (being cognizant of vulnerable populations)
- Informed consent will be sought from each prospective subject
- Research plan makes adequate provision for monitoring the data
- Adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data
- Additional safeguards have been included in the study to protect the rights and welfare of these subjects
Required Representation on the IRB Committee

Members of each committee include UC Davis faculty, clinicians, staff, students, and community members. Each IRB committee consists of at least five regular, voting members. The IRB members are required to be sufficiently qualified through experience and expertise, for reviewing research proposals in terms of regulations, applicable law and standards of professional conduct and practice, and institutional commitments. Each IRB has at least one member whose primary concerns are in nonscientific areas. For further information refer to (IRB SOP #823).

IRB Committee Meeting Schedule

Application packet submission deadlines for Full Committee (A, B & C) review are posted on the IRB Administration web site: http://research.ucdavis.edu/c/cs/hrp/irb-mtg. Committees meet twice monthly and deadline dates are listed for each meeting. Protocols must be received no later than 5:00 pm on the deadline day. Any protocol received after the deadline will be automatically placed on the next deadline schedule. Incomplete applications will not be scheduled for a meeting. Since studies submitted for Expedited Review or Exempt studies are not scheduled for review at a convened meeting there are no deadlines posted. However, there are deadlines for submitting the renewals for these studies, which are included in the renewal notice.

Central IRB

The Central Institutional Review Board Program (CIRB) is sponsored by the National Cancer Institute (NCI) in consultation with the DHHS Office of Human Research Protections. CIRB’s primary goal is to improve access to clinical trials for patients and their physicians by enabling local IRBs to rapidly approve NCI-sponsored multi-site trials through the use of a facilitated process. CIRB enhances the protection of research participants by providing consistent, expert review at the national level before the protocol is distributed to local investigators.

The Adult CIRB reviews all Phase 3 Cooperative Group Trials from the SWOG (Southwestern Oncology Group), RTOG (Radiation Therapy Oncology Group), NSABP (National Surgical Adjuvant Breast Project), NCCTG (North Central Cancer Treatment Group), ECOG (Eastern Cooperative Oncology Group), CALGB (Cancer and Leukemia Group B), and ACOSOG (American College of Surgeons Oncology Group), as well as any other protocols opened in the Cancer Trials Support Unit.

The Pediatric CIRB reviews all NCI-approved COG (Children’s Oncology Group) Phase 2, 3, and Pilot protocols.

For more information on CIRB, visit: http://research.ucdavis.edu/c/cs/hrp/cirb/cirb

23 http://research.ucdavis.edu/gt/irb-sop
Reliance IRB Program

To streamline IRB review of multi-UC Campus research, UC Davis has entered into an arrangement with other UC campuses. This arrangement will allow research to be reviewed by a single UC IRB for research that is conducted at multiple UC campuses (http://research.ucdavis.edu/c/cs/hrp/uccr).

Types of Review Submissions

**Exempt Review**

Research studies that expose human subjects to a very small risk; no more than they would encounter in daily life (e.g. telephone survey, taste and food quality evaluation and consumer acceptance studies, studies conducted in established educational setting involving normal educational practices) may be determined to be exempt under 45 CFR 46.101(b)(1)-(6), 45 CFR 46.301(a), 45 CFR 46.401(b) or a complete list of exemption categories refer to: IRB SOP #32. Only the IRB Chairs, the IRB Director, Assistant Director, or reviewer designated in advance by the IRB Executive Committee may determine if a study qualifies for an exemption. Research subjects enrolled in an Exempt research study are entitled to the same subject protections and ethical standards as outlined in The Belmont Report.

**Expedited Review**

Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following nine categories below, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR46.110 and 21 CFR 56.110.

- Certain clinical studies of medical devices, such as:
  - Research with Non-Significant Risk medical devices for which IDE is not required, or if medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.
- Prospective collection of biological specimens by noninvasive means.
- Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves.
- Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis for retrospective chart reviews).
- Collection of data from voice, video, digital or image recordings made for research purposes.

24 http://research.ucdavis.edu/gt/irb-sop
• Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies

• Continuing review of research previously approved by the fully convened IRB if the research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects. No subjects have been enrolled and no additional risks have been identified; or the remaining research activities are limited to data analysis.

• Continuing review of research not conducted under the IND application -or- where IND exemptions do not apply but the IRB has documented that the research involves no greater than minimal risk and no additional risks have been identified.

The complete list of categories of research that may be reviewed by the IRB through an expedited review process can be found at http://www.hhs.gov/ohrp/policy/expedited98.html. The IRB may use an expedited procedure to conduct initial review of research provided none of the research activities fall under any of the general restrictions and present no more than minimal risk to human subjects. Expedited procedures cannot be used for classified research, or when identification of the participants or their responses would reasonably place them at social or legal risk. Previously approved research that has undergone minor changes may qualify for an expedited review.

All expedited studies are reviewed by the IRB at least once per year. An expedited review consists of a review by the IRB chair or Chair’s designee. The reviewer, however, may not disapprove the research. Disapproval is only determined by the full IRB Committee. Additionally, the reviewer may refer the study to the full committee for further review. For more information please see IRB SOP# 33, Expedited Review25.

**Full Committee Review**

Full Committee Review is required for any research involving human subjects that does not fall into either exempt or expedited review or is considered having greater than minimal risk. This is the most rigorous level of review. All such research requires that initial and continuing review be conducted by the IRB at a fully convened meeting. UC Davis IRB must determine that all of the requirements for approval are satisfied as outlined in 45 CFR 46.111(a)(1-7)(b) (also see IRB SOP #34, Criteria for Approval26). IRB Members must apply these criteria during the review process and document that all requirements for approval have been satisfied.

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25 [http://research.ucdavis.edu/gt/irb-sop](http://research.ucdavis.edu/gt/irb-sop)
26 [http://research.ucdavis.edu/gt/irb-sop](http://research.ucdavis.edu/gt/irb-sop)
IRB Clinical Full Committee application instructions & guidance specifies information that the Committee reviews27.

Information reviewed by IRB for Full Committee Application:

- Specific Aims, Backgrounds and Significance
- Scientific Design
- Use of Drugs, Devices and Biologics
- Research Methods and Procedures
- Inclusion/Exclusion Criteria for subjects
- Statistical Analysis and Data Monitoring
- Subject Privacy and Confidentiality
- Recruitment of Subjects
- Subject Compensation and Costs
- Potential Risks/ Discomforts and Benefit for Subjects
- Informed Consent/Assent Form or Waiver or Alteration of Informed Consent
- Disclosure of Personal and Financial Interest
- Federal Grant or Sponsor Protocol, as applicable
- Ancillary Committee Approvals

How to submit to the IRB

NEW Full Committee and Expedited submissions have to be signed-off by the SOM Dean’s Office before they can be accepted for the IRB review.

The IRB Administration accepts submissions via electronic media through the eDocs system which is accessible at http://www.research.ucdavis.edu/edocs.

To upload documents, click on “Drop off your documents” link and enter name, e-mail and other required information. To conduct any future communication, IRB will issue eDoc ID. All IRB forms can be found at: http://research.ucdavis.edu/f/f#Forms-%20IRB%20Admin.

27  http://research.ucdavis.edu/f/d/irb/Guidance_Application_Clinical_Full_Board12.5.11LT.pdf
Content of IRB Submissions

NEW STUDIES

- IRB Application Form with required signatures
- Sponsor’s or Investigator’s Protocol
- Research Personnel List
- PI and Co-PI Current Biosketch (required only if non-faculty)
- Description of Study (DOS)
- Recruitment materials (flyer/advertisement/letter/etc)
- Consent Form
- Assent Form (for minors Ages 12-17 yrs.) – if applicable
- Letter of Information (for minors Ages 8-11 yrs.) – if applicable
- Oral Consent/Screening Script
- Surrogate Self-Assessment Checklist – if applicable
- Capacity Assessment Checklist – if applicable
- Debriefing Script (for Deception Studies)
- Waiver or Alteration of Informed Consent
- Waiver of HIPAA Authorization
- Vulnerable Populations as Participants form(s)
  - Children/Minors/Viable Neonates
  - Pregnant Women/Human Fetuses/Neonates
  - Prisoners
- Questionnaires/Assessments
- Interview Scripts
- Sponsor Information Form (industry-sponsored only)
- Investigators Brochure
- Drug/Package Insert
- Investigational Drug/Botanical/Biologic/Dietary Supplement form (and IND &/or FDA communication)
- Investigational Device form (and IDE &/or FDA communication)
- Approval by other Committees (as applicable)
  - Cancer Center Scientific Review committee (for all cancer related studies)
  - Radiation Use Committee (for any studies using radiation such as x-rays; or involving radioactive markers or test articles or products)
  - Operating Room Resource Committee (for all studies involving the surgical suites)
  - Conflict of Interest Committee (for any study in which the PI has a positive Financial or other Interest in the Sponsor/Investigational Product or other perceived financial/personal interest)
- For Federally Funded Grant Studies submit a complete copy of the grant
RENEWAL STUDIES

- Renewal Form with required signatures
- Progress Report
- Deviations Table
- Adverse Event Table
- Data Safety Monitoring Board (DSMB) Reports (if applicable)
- Sponsor Report
- Previously approved and signed Modification Forms (since last approval/renewal)
- Stamped (previously approved) DOS
- Marked DOS (if changes are made)
- Clean DOS*
  - Stamped (previously approved) Recruitment materials/flyers
  - Marked Recruitment materials/flyers (if changes are made)
  - Clean Recruitment materials/flyers and Screening Scripts*
  - Stamped Consent Forms / Assent Forms
  - Marked Consent Forms / Assent Forms (if changes are made)
  - Clean Consent Forms / Assent Forms*
- Sponsor Information Form (industry-sponsored only)
- Other / Miscellaneous Materials

*The clean version will receive a current IRB stamp upon approval.

MODIFICATIONS/AMENDMENTS

- Modification Form
- Marked Research Personnel List
- Clean Research Personnel List
- Marked DOS
- Clean DOS*
  - Marked Recruitment materials/flyers
  - Clean Recruitment materials/flyers and Screening Scripts*
  - Marked Consent Forms / Assent Forms
  - Clean Consent Forms / Assent Forms*
- Other / Miscellaneous Materials

Data and Safety Monitoring Plans

UC Davis IRB requires investigators proposing research involving human subjects to include with each application (with the exception of Exempt research) a plan for monitoring the data to ensure the safety of subjects. The plan may be described by the sponsor in the corporate or cooperative group protocol or by the investigator in
an investigator-initiated protocol. The Data and Safety Monitoring Plan (DSMP) must be presented in sufficient detail for the IRB to determine whether it is appropriate for the research (IRB SOP #28, Data and Safety Monitoring Plans).

A DSMP is unique to each project, should be tailored for the project commensurate with the potential risks and with the size and complexity of the project. Appropriate DSMPs may fall anywhere along a continuum from monitoring by the principal investigator or group of investigators to the establishment of an independent Data and Safety Monitoring Board (DSMB).

UC Davis Policy and Procedure Manual (Chapter 240, Section 30) specifies minimal DSMP content:

1) An assessment of the level of risk of the investigation;
2) Identification of the individual or entity responsible for monitoring the study;
3) Description of the steps that will be taken to monitor subject safety and review data accuracy;
4) A statement regarding the frequency of monitoring and review;
5) A discussion of anticipated adverse events (including severity scale and attribution scale); and
6) A plan for reporting adverse events.

UC Davis CTSC offers regulatory and data safety monitoring/auditing services for investigator-initiated trials. Please contact CTSC Clinical Trials Resource Group at www.ucdmc.ucdavis.edu/clinicaltrials

UC Davis Informed Consent Forms

The consent document provides the participant with information such as time commitments, treatment procedures, potential drug risks/benefits, potential costs and confidentiality considerations, all of which will help a potential subject make educated decisions about whether to participate in a clinical trial. (IRB SOP #19, Informed Consent).

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28 http://research.ucdavis.edu/gt/d/irb/
30 http://research.ucdavis.edu/gt/d/irb/
To create a Standard Consent, refer to the IRB Administration’s MODEL CONSENT FORMS that are available on the IRB Administration Web site.31

Types of Consent Forms at UC Davis

- Biomedical Consent Form (studies involving drug, biologic, or device)
- Social and Behavioral Consent Form (Psychological studies)
- Assent Form for Minors in Research (used for children 12 – 17 yrs old)
- Consent for the Use of Leftover Biological Specimens (only for studies where the researcher is collecting normally discarded tissue removed from non-research related surgeries)

Please be sure that you use the current consent template from the IRB website, as the standard UC Davis Consent language and formats are updated frequently. When receiving a consent form from industry sponsors, you will need to incorporate the information into our UCD standard consent format. It is mandatory that the person creating the consent integrate the information from the sponsor consent into the UC Davis Standard Consent so that all required information regarding the study is incorporated. Next, the new version of the consent form must be approved by the sponsor prior to IRB submission. However, the UC Davis Institutional Review Board has final jurisdiction over what is contained in the informed consent.

Common Mistakes in Informed Consent

1) Incomplete and/or inconsistent information
2) Language is too complex
3) Recruitment and consent process is not well explained
4) “De-identified” not a meaningful term by itself
5) Standard of care procedures vs research procedures are not clearly described

31 http://research.ucdavis.edu/f/f#Forms-%20IRB%20Admin
Consent vs Clinical Trial Agreement

<table>
<thead>
<tr>
<th>The Consent Form:</th>
<th>The Clinical Trials Agreement:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is not a contract for exchange of services for payment, but an acknowledgement.</td>
<td>Is a contract for services provided by the University in exchange for payment: required only when we are being paid by a Sponsor to conduct a trial.</td>
</tr>
<tr>
<td>It is between the University and the Patient/Subject.</td>
<td>It is between the University and the Sponsor (the PI and the study subjects are not parties to the contract).</td>
</tr>
<tr>
<td>Necessary for regulatory compliance purposes.</td>
<td>Is necessary to cover the legal risks between the parties in exchanging services for payment.</td>
</tr>
<tr>
<td>Project specific.</td>
<td>May be a template or master and not project specific.</td>
</tr>
<tr>
<td></td>
<td>Subject injury language is only required in Sponsor-Initiated studies.</td>
</tr>
</tbody>
</table>

Subject injury language in consent and contract often presents a difficult point in negotiations with the industry sponsors.

**Industry-Initiated trials**

UC is required to provide services for injuries that occur during clinical trials. This is our obligation to the patient/subject, reflected in the consent form.

The sponsor is required to reimburse UC for the cost of these services if the injuries are related to the study materials or study procedures required by the sponsor protocol. This is a sponsor obligation to UC, and reflected in the Clinical Trial Agreement. Either insurance or UC will pay for the injuries not directly related to study materials.

**Investigator-Initiated trials**

UC is required to provide services for injuries that occur during clinical trials. This is our obligation to the patient/subject, reflected in the consent form. Either insurance or UC will pay for these services.

For specific determination of the payee for research-related injuries, please contact the HS Compliance office at 916-734-8338.
The Experimental Subject’s Bill of Rights

The California Health and Safety Code Section 24173(a) requires that the Experimental Subject’s Bill of Rights be given to subjects prior to consent, and also requires investigators to secure the subject’s signature and the date signed on the Bill of Rights. This signed document, along with the signed copy of the consent form, must be provided to all subjects. This form comes in multiple languages (http://research.ucdavis.edu/f/f#Forms-%20IRB%20Admin).

For the full text of Bill of Rights see Appendix 3.

HIPAA (Health Insurance Portability & Accountability Act)

The HIPAA form is provided during the consenting process. **This form does not have to be submitted to the IRB.** State and Federal privacy laws protect the use and release of an individual’s health information. HIPAA is a federal law that applies to health care providers, health plans, and health care clearinghouses. These are covered entities (University of California is a hybrid Covered Entity with both covered and non-covered functions). By signing this form, the subject is authorizing their health care providers to release health care information. Authorization elements required by HIPAA includes description of information to be used, name of class of persons authorized to disclose information, name of recipients of information, description of research purpose, expiration date of authorization and the right to revoke authorization.

Personal Health Information (PHI) includes information contained in their medical records (e.g. physical or mental health, diagnosis and/or treatment) and information that can identify them, that includes personal identifiers (e.g. name, address, email address, social security number, DOB, full face photo, medical record number).


The full text of the form is provided in Appendix 4.

Other Committees and Approvals

Conflicts of Interest Committee (COIC)

State and Federal law requires university employees responsible for the design, conduct, or reporting of sponsored projects to disclose their personal interests related to the project. When a financial disclosure is received from an investigator indicating a personal financial interest related to the subject of the research, the disclosure is submitted to the Conflict of Interest Committee for review.
The COIC is comprised of faculty members from different disciplines across campus and the Health System. The COIC reviews the disclosure to determine whether an actual or potential conflict of interest exists and, if so, recommends how the interest can be reduced, managed or eliminated so the research can proceed. The Research Compliance & Integrity unit provides administrative support to the COIC.

Not all financial interests constitute conflicts of interest. Additionally, having conflict of interest is not fatal to a research proposal. However, if the COIC determines there is an actual or potential conflict, the research can proceed only if the conflict is managed, reduced or eliminated. Some management strategies include public disclosure of the financial interest, oversight by a management sub-committee and divestment of the interest.

Process flowcharts for filing and review of financial disclosure documents for government sponsored projects, non-government sponsored projects and projects involving human subjects are available online at http://research.ucdavis.edu/c/cs/ci

Radiation Use Committee

Health Physics\(^\text{32}\) is responsible for overseeing the safe and effective use of ionizing radiation within the Health System, X-Ray machines and radioactive materials used at the University of California, Davis Medical Center and the Primary Care Network for diagnostic and therapeutic purposes, as well as in research and development. When an investigative procedure involves exposure of human subjects to ionizing radiation, including radiation from machines, or radioactive materials, Federal, State, and University regulations require an additional approval by the UCDMC Radiation Use Committee (RUC). This committee verifies the radiation exposure calculations, which, together with other information, determine the potential risks.

The committee meets at least quarterly and consists of at least nine members, including five of the medical staff, the Medical Center Radiation Safety Officer, and a representative from Administration. At least one medical staff member of the committee is recognized as a specialist in each of the following areas: Nuclear Medicine, Diagnostic Radiology, and Therapeutic Radiology.

**Human Radiation Use Research Application (Form 5)** (http://intranet.ucdmc.ucdavis.edu/safety/hp/radprotocol.html) should be completed and submitted when requesting authorization to:

- Use Radioactive materials/radiopharmaceuticals in human research.
- Use diagnostic x-ray, fluoroscopy, or any other external radiation source in human research.

\(^{32}\) http://intranet.ucdmc.ucdavis.edu/safety/hp/
Protocol Exemption from Radiation Use Committee Review form (Form 35) should be submitted if the study meets specific exemption criteria, such as if the study has been already reviewed by any of the national cooperative groups. It must be signed by the principal investigator of the study, and submitted to Health Physics (Radiology) for review. It will then be signed by a representative from Health Physics and faxed back to the research team to be included in the New Submission packet.

Biological Use Authorization

All University research involving recombinant DNA molecules (rDNA) shall be conducted in compliance with NIH Guidelines for Research involving Recombinant DNA Molecules\(^{33}\) regardless of the funding source. The following activities require approval of a Biological Use Authorization (BUA) by the Institutional Biosafety Committee\(^{34}\).

- Research involving recombinant DNA technology, except projects that are exempt under the NIH Guidelines for Research Involving Recombinant DNA Molecules.
- Work with materials that are infectious (or potentially infectious) to plants, animals, or humans (including replication-defective viral vectors).
- Working with any material that falls under the Cal OSHA Bloodborne Pathogen Standard. This includes any work with human cell lines, human blood or blood products, and human body fluids. At UC Davis, work with non-human primate (NHP) cells, established NHP cell lines, and NHP blood or blood products also requires a BUA.
- Storage of biohazardous materials that are not being used.

The BUA form is available online\(^{35}\).

BUA Amendments should be submitted to the Institutional Biosafety Committee for any change in the original Biological Use Authorization, including changes to personnel, location, agents or procedures.

Stem Cell Research Oversight Committee

The Research Compliance & Integrity unit\(^{36}\) of the UC Davis Office of Research provides administrative support on issues pertaining to stem cell research and

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\(^{36}\) [http://www.research.ucdavis.edu/u/a/rci](http://www.research.ucdavis.edu/u/a/rci)
supports the **Stem Cell Research Oversight committee** (SCRO). SCRO approves, requires modification, or disapproves human adult and embryonic stem cell research at UC Davis and the UC Davis Health System. It also reviews all research involving human stem cells at least once each year. The Vice Chancellor for Research selects and appoints members of the SCRO and provides staff support to the SCRO. Committee members are comprised of individuals with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical issues in stem cell research. It includes at least one non-scientist member of the public who is not employed or remunerated by UC Davis and who is not part of the immediate family of a person who is affiliated with the institution (for details, see SCRO SOPs).


SCRO SOPs are located at: [http://research.ucdavis.edu/gt/fgpr#gt-scro](http://research.ucdavis.edu/gt/fgpr#gt-scro) (scroll to the end of page).

**Scientific Review Committee (SRC) (Cancer Center Only)**

The Scientific Review Committee oversees the oncology clinical trials program by reviewing all cancer-related clinical protocols to assure feasibility, research quality, and statistical validity *prior* to submission to the IRB. The SRC thus provides a centralized mechanism for prospective evaluation of scientific merit and prioritization of clinical trials, resource allocation and accrual monitoring. SRC meetings are held on the first Thursday of each month.

Scientific Review Committee members are nominated by the Associate Director of Clinical Research and approved by the Cancer Center Director, based on the following criteria:

1. Experience with clinical research trials  
2. Expertise in medical, pediatric, surgical, and radiation oncology, cancer drug development, nursing, molecular biology, or data management  
3. Expertise in clinical pharmacology and in investigational drug requirements  
4. Expertise in biostatistics  
5. Familiarity with the UCDCC research base

Twenty members from several academic departments constitute the regular voting committee.
SRC Submission process

Prior to SRC review, proposed clinical research protocols are vetted through disease site groups. National Cooperative Group trials and trials conducted under the NCI-supported California Cancer Consortium can be submitted without disease site group review. Next, the principal investigator submits a full protocol to the SRC Administrative staff electronically, along with a completed SRC Protocol Submission Form. The application must be received 15 working days prior to the next meeting. To obtain the form contact SRC Coordinator at 916-734-2596.

IND and IDE submissions to the FDA

Studies Involving Investigational Drugs

If a study involves the use of a non-marketed drug, or an already-marketed drug that does not meet all of the requirements for exemption from FDA regulatory requirements\(^37\), the investigator must submit an IND application to the FDA for review in order to obtain permission to conduct the proposed research. For example, if a drug is intended to be used for an indication other than what was originally approved, a new IND may be required. Similarly, if a dietary supplement is used for diagnosis, treatment or mitigation of a disease, an IND may be required. A dietary supplement could be sold over-the-counter, and yet for the purposes of clinical research studies, it may be considered a drug. Proposals for studying extracts from plants may be classified as botanical drug products, and will be reviewed by the FDA Botanical Review Team.

The process and format for submitting an IND application is defined in 21 CFR 312.23, “IND Content and Format.” The FDA must review the application within 30 days of formal receipt, and will either allow the IND to go into effect or place the study on clinical hold until the regulatory sponsor satisfactorily responds to all the issues raised by the FDA prior to initiating the research.


Studies Involving Investigational Devices

For clinical studies of investigational devices, an assessment of risk associated with the use of the investigational device defines the mechanism for regulatory oversight. If the study involves a non-significant risk device (NSR device), and if the IRB approves the study, the study is considered to have an approved IDE. This is often referred to as an abbreviated IDE. The IRB determines if the device is NSR or SR.

If the study involves a significant risk device (SR), an IDE application must be submitted for review and approval by the FDA. As with an IND application, the FDA has 30 days to either approve the IDE or notify the sponsor that the investigation may not begin.

The process and format for submitting an IDE application is defined in 21 CFR 812.20, and can be found on CTSC website: [http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/index.html](http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/index.html).

Clinical studies involving *investigational diagnostic devices* are normally exempt of the IDE regulations, except when the testing requires an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a subject, or is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure. In the era of personalized medicine, there will be an increased use of in vitro diagnostic (IVD) tests in clinical studies to define or withhold therapy, assess future risk of various disease states, and assess safety and efficacy of therapeutics. Depending upon the criticality of the decisions made by the IVD, these studies could range from being exempt from the IDE regulations, to being designated as a significant risk device requiring an approved IDE application by the FDA.

**Pre-approval Financial Requirements**

These include Coverage Analysis, Feasibility Assessment, Budgets and Contracts

**Coverage Analysis**

Coverage Analysis[^38] is a process of identifying what study-related procedures and services can be paid by the third party payor, including Medicare, and what should only be paid by the study sponsor. In order to bill the third-party payors, a clinical study must meet qualifying criteria. At UC Davis we only use Medicare coverage criteria, and extend this to all insurance companies. Insurance policies vary in their coverage of clinical research; therefore, it is important that the study participant confirm coverage with his/her individual insurance company. The Coverage Analysis consists of two documents, a QCT (Qualifying Clinical Trial) Form and a Billing Grid. This process is outlined in CTSC Clinical Research SOP #4[^39].

[^38]: [http://intranet.ucdmc.ucdavis.edu/researchbudgeting/#coverageanalysis](http://intranet.ucdmc.ucdavis.edu/researchbudgeting/#coverageanalysis)
Qualification Process

The first step in Coverage Analysis is the qualification of a clinical trial. It is a self-certification process for principal investigators to certify to Medicare that a research study meets certain Medicare qualifying criteria. When the research study is self-certified as meeting these criteria, the study is a “qualifying clinical research study.” This means that Medicare (and by extension, other insurance companies) will cover routine and expanded patient care during the study. Routine care is also called “standard of care” and defines procedures/services that would be performed absent of a clinical trial. The expanded care includes additional services such as clinically necessary monitoring, administration of the clinical study article (drug or device) and procedures for diagnosing, treatment and mitigation of side effects resulting from the patient’s participation in the clinical study and diagnosis or treatment of complications (Medicare’s Clinical Trial Policy, NCD 310.1).

QCT (Qualifying Clinical Trial) Form takes you through the qualification process. The current version of the form can be found on CTSC intraweb.

The PI reviews and signs the form. Misrepresentation of qualification may lead to denial of Medicare coverage of the routine costs. In the case of such a denial, the Medicare beneficiaries enrolled in the trial would not be held liable (i.e., would be held harmless from collection) for the costs. Where appropriate, the billing providers would be held liable for the costs. Fraud investigations of the billing providers and the trial’s PI may be pursued.

Billing Grid Process

If the study qualifies for Medicare coverage, the clinical events specified in the protocol are listed in the Billing Grid (Excel spreadsheet). Each procedure is reviewed in detail to determine which would be reimbursed by Medicare and why. The preparation of the Billing Grid requires knowledge of CPT codes and Medicare coverage guidelines. Each CPT code listed in the Billing Grid is reviewed for national and local coverage determinations. Medicare will not cover routine costs in a non-qualifying trial, that are paid for by the sponsor, promised free in the informed consent document, not ordinarily covered by Medicare or for studies that are solely for data collection or analysis.

For assistance with billing grids, please contact CTSC Clinical Trials Resource Group.

Feasibility Assessment

A Feasibility Assessment provides a guideline for assessing the protocol for financial, scientific and patient enrollment feasibility. Per CTSC SOP #5 and #6, this is a mandatory document at UC Davis and requires approval and signature by

40 http://intranet.ucdmc.ucdavis.edu/researchbudgeting/#coverageanalysis
the Department Chair. The Feasibility Assessment Form can be found on CTSC intraweb\textsuperscript{41}.

For more details on Feasibility Assessment see CTSC Clinical Research SOP #5 and #6\textsuperscript{42}.

**Budgets**

At UC Davis, the internal study budgets are prepared using the *Unified Budget Template*\textsuperscript{43}. The template has been developed over a period of two years by the Budgeting and Billing taskforce. The template consists of following components:

- Start-up Costs
- Close-out Costs
- Invoicable costs (yearly or per occurrence)
- Per patient costs

The first three categories are based on the anticipated time and expense to conduct these activities. Sample time brackets are provided for guidance.

Per patient costs are composed of protocol-related tasks, procedures and hospital services. The Coverage Analysis is necessary to determine what services should be included in the per patient costs. These are services that will be paid by the sponsor, and not by third-party payors (insurance companies). Please refer to your Coverage Analysis to incorporate correct line items in the per-patient grid.

Next, using the Unified Budget Template (internal costs) the budget is negotiated with the sponsor. The final budget will reflect the negotiated rates that the sponsor will pay.

For assistance with budget preparation, please see CTSC SOP#8\textsuperscript{44} or contact the Budget Analyst at HS Contracts – Clinical Trials (\url{http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/contactus.html}).

**CDA and Contract Negotiations for Industry-Sponsored Studies**

1) **Initial Contact.** A sponsor or a PI can initiate contact regarding interest in a protocol (a PI written protocol for PI initiated studies or a Sponsor created protocol for Sponsor initiated studies).

\textsuperscript{41} \url{http://intranet.ucdmc.ucdavis.edu/researchbudgeting/#feasibilitycheck}
\textsuperscript{42} \url{http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml}
\textsuperscript{43} \url{http://intranet.ucdmc.ucdavis.edu/researchbudgeting/#prepareinternalbudgets}
\textsuperscript{44} \url{http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml}
2) **Confidentiality Agreement.** In some instances a sponsor will send a Confidential Disclosure Agreement (CDA) prior to sharing a protocol or confidential documents. If a PI receives a CDA, the request should be submitted to Health System Contracts - Clinical Trials for negotiation (http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialcontracts/). Under very limited circumstances, the PI may sign the confidentiality agreement on their own behalf as a personal agreement; however, this will not allow sharing of the protocol with other UC personnel and may conflict with other PI obligations, so it is discouraged. Confidentiality agreements are not required by all Sponsors. Some Sponsors may already have Master Confidentiality Disclosure Agreements with the University.

3) **Clinical Trial Budget.** If there is some question as to whether the project meets the definition of a clinical trial, it is best to contact Health System Contracts – Clinical Trials Office prior to budget negotiations. Once it has been verified that the protocol meets the definition, the PI and the department are responsible for preparing a preliminary internal cost budget, negotiating a final sponsor budget and submitting to the Department Chair for signature. This negotiated budget will become part of the contract packet and submitted the SOM Dean’s Office for approval and forwarded to HS Contracts-Clinical Trials office, where the Budget Analyst will review for policy compliance and approve the final internal cost budget.

4) **Clinical Trial Contract Request Packet.** The department prepares the internal contract packet and routes to the Dean’s Office School of Medicine Sponsored Programs for approval. The complete list of forms is available on line45.

5) **IRB Review Packet.** The IRB packet is submitted separately to the IRB for review and approval. This review may be conducted concurrently with contract negotiation, but must be completed prior to Institutional Signature of the clinical trial contract.

6) **Dean’s Office Review.** The Dean’s Office School of Medicine Sponsored Programs reviews, approves the contract packet, and routes to the Health System Contracts – Clinical Trials Contracts Office. The Clinical Trials Contracts Office negotiates and has final signature authority for the agreement.

7) **Contract Office Receipt and Assignment.** Once the contract packet is received by the contracts office it is assigned to an analyst for review, negotiation and final execution. The analyst will work with the department contact if there are missing elements or delays with negotiations. Conflict of interest documents are reviewed and submitted to Conflicted of Interest Committee for approval as appropriate. This review may be concurrent with contract negotiation, but must be approved prior to IRB approval and prior to Institutional Signature of the contract.

8) **Contract Office Initial Review.** The analyst will review the contract for consistency with UC policy, state and federal law, using the budget, protocol and internal forms as necessary. The analyst may also seek consultation with Risk Management, UCDHS Legal, IRB, UCOP or other sources as necessary to complete the initial review.

9) **Contract Office First Comments to Sponsor.** The analyst will send a marked copy of the agreement to the sponsor with a copy to the PI and department. Where reasonable, the analyst will keep the PI and department copied on correspondence with the sponsor or provide reasonable updates on the agreement.

10) **Contract Negotiation.** The analyst may need to consult with the department, PI, IRB, UCDHS Legal, Risk Management, Innovation Access, UCOP and other sources during the negotiation process in order to move the agreement forward and ensure compliance with UC policies and applicable laws.

11) **End of Negotiation and PI Approval.** Once there is agreement between the analyst and the sponsor, the analyst will send the agreement to the PI and department contact for final review and approval. If changes are requested, the analyst will negotiate any remaining issues with the sponsor. The contract will be held at this point until the PI has approved or the department contact certifies PI approval.

12) **Sponsor/Institutional Execution.** Once approved by the PI, the agreement will be sent for signature, typically starting with the PI signature of acknowledgement to the contract. After the PI signs the agreement and evidence is available that the IRB (COI Committee, and other committees when necessary) has approved the project and all administrative requirements are met, the Director of Health System Contracts signs the agreement on behalf of UC. Typically the Sponsor signs last and the agreement is then fully executed.

13) **Final Contract Distribution.** After the fully executed agreement is returned to Clinical Trials Contracts, the agreement is scanned, processed in the database, then electronically distributed to Extramural Accounting, the School of Medicine Dean’s Office Sponsored Programs, the PI and the department contact, the IRB and other parties as required.

14) **Contract Maintenance.** After the contract is executed, Clinical Trials Contracts will be responsible, upon request from the Department, to negotiate and execute amendments to the project period, budget, or other required changes to the contract as agreed between the sponsor and the PI and department. Such requests must originate from the department, rather than directly from the sponsor.
15) **Contract Closeout.** Once the project is terminated by the sponsor or the contract end date expires, Clinical Trials Contracts will note the termination or expiration of the agreement and close the file. Closing the agreement file does not close the project account, and this closeout process must be done through Extramural Accounting. Clinical Trials Contracts must retain the agreement for the period of time designated in the agreement or if not so designated the period legally required. The PI and department must retain the project records for the period of time designated in the agreement.

**Advance Accounts**

If the sponsor agrees in writing (e-mail is acceptable) to provide funding in the amount of start up costs, the PI can open an advance account. These accounts can be used to record administrative costs for study set up prior to execution of the entire Clinical Trial Agreement. To set up the advance account, contact HS Contracts-Clinical Trials Contracts (http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/requestforms.html).

**DaFIS Accounts and Bulk Accounts**

Once the Clinical Trials Contract is executed by both UC Davis and the sponsor, the HS Contracts office notifies Extramural Accounting. Extramural Accounting sets up the extramural account. Once the DaFIS (Koali) account is set up, the financial manager or CRC opens the Bulk Account. The Bulk account is used to place hospital/clinic research study specific charges. Salaries and other expenses are posted directly to DaFIS. To open a Bulk Account see: http://intranet.ucdmc.ucdavis.edu/researchbudgeting/#bulkaccounts.

**Regulatory Steps Post-IRB Approval**

**Clinicaltrials.gov**

The ClinicalTrials.gov Protocol Registration System (PRS) is a web-based tool developed for submitting clinical trials information to ClinicalTrials.gov (www.clinicaltrials.gov).

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a “responsible party” (i.e., the sponsor or designated principal investigator) register and report results of certain “applicable clinical trials.”

“**Applicable clinical trials**” generally include interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA
regulation, meaning that the trial has one or more sites in the U.S, involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE).

- **Trials of Drugs and Biologics:** Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation.

- **Trials of Devices:** Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

PRS users enter information about their clinical trials, ensuring that the information is correct, readily understood by members of the public, and updated in a timely manner. Protocol information must be clear and informative, and information must be consistent with the ClinicalTrials.gov Protocol Data Element Definitions (http://prsinfo.clinicaltrials.gov/definitions.html).

ClinicalTrials.gov reviews protocol information for apparent validity, meaningful entries, logic and internal consistency, and formatting. It is the responsibility of the data provider to ensure that records are consistent with these criteria. The public posting of a registration record by ClinicalTrials.gov does not necessarily mean that all of these criteria have been met. At times, ClinicalTrials.gov may note problems and request revisions after a record has been posted publicly.

It is the **Study Sponsor**’s responsibility to register the trial with ClinicalTrials.gov.

- You are considered the study Sponsor if you wrote the study protocol (Sponsor Investigator-Initiated).
- If the study protocol was sent to you by an industry sponsor, then the industry sponsor will have the responsibility to register the trial.
- If industry is supplying a drug or device for your study, but you are the author of the study, then it is your responsibility to register your trial.
- If you have received grant funding to conduct a clinical trial then you, as the awardee, are considered the Sponsor for that trial.

In order to register your clinical trial with ClinicalTrials.gov you will need to request User access. Go to the UC Davis Clinical & Translational Science Center (CTSC) website and complete an Application For Resource Use (AFRU) requesting “ClinicalTrials.gov User Access” (www.ucdmc.ucdavis.edu/ctsc/). The Administrator will assign a User ID and send further instructions to get your account established.

Subject Enrollment

When a potential subject has been identified, an appointment should be scheduled to discuss the study and to obtain informed consent. When obtaining informed consent, the subject should be given ample time to read the ICF, ask questions, and to decide whether he/she would like to participate. The subject must be shown and informed of the Experimental Subject’s Bill of Rights.

After obtaining informed consent, the subject should be given a copy of the signed document. The signed original must be retained by the investigator and made available for review by the sponsor, their representative CRO (Contract Research Organization), the IRB, and/or FDA. Additionally, the study subject must also sign and receive a copy of the study specific Authorization for Release of Protected Health Information for Research Purposes form (Appendix 4).

Adverse Event Reporting to the IRB

Please review IRB Training Presentation “Reviewing and Reporting AEs”\textsuperscript{46}.

Unanticipated risks are sometimes discovered during the course of research. The PI is responsible to notify the IRB of Adverse Events and Serious Adverse Events (SAEs) or injury to participants while on a clinical trial. Investigators will be asked to provide their opinion as to whether any proposed changes need to be made in the description of the study or the consent forms(s). Investigators will also be required to make these assessments for the severity of the event, and relationship to the study drug.

This information may impact the risk/benefit ratio, and based on such information, the IRB may need to reconsider its approval of the study, require a modification to the study, or revise the continuing review timetable. The IRB is also responsible for ensuring that reports of unanticipated problems involving risks to research participants or others are reported to the FDA. Such reporting may go through the investigator to the sponsor to the FDA, or in case of investigator-initiated studies from sponsor-investigator to the FDA.

\textbf{Adverse Event (AE):} An adverse event is an undesirable and unintended event occurring as a result of therapy or other intervention (e.g., headache following spinal tap or intestinal bleeding associated with aspirin therapy). It also includes any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the

\textsuperscript{46} http://research.ucdavis.edu/gt/d/irb/reviewing-and-reporting-aes/view
research. For billing purposes it is important to know if the event is directly related to research (see Coverage Analysis above). It is directly related if:

- Could not readily have been produced by the research participant’s clinical state.
- Could not readily have been due to environmental or other interventions.
- Follows a known pattern of response to intervention.

**Serious Adverse Event (SAE):** Events are classified as serious if they meet any of the following criteria:

- Results in death or any life-threatening event that places the subject at immediate risk of death from the event as it occurred
- Any event that requires or prolongs in-patient hospitalization.
- Any event that results in persistent or significant disability/incapacity.
- Any congenital anomaly/birth defect diagnosed in a child of a subject who participated in this study and received study drug.
- Other medically important events that in the opinion of the investigator may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

**Unanticipated AE:** Any adverse experience, the frequency or severity of which is not consistent with the current consent form or investigator brochure.

**Unanticipated Problem Involving Risk to Participants or Others:** Any unanticipated event involving any aspect of a research study involving anyone (participants, research staff, or others not directly involved in the research) that increases a risk to the persons involved.

**Reporting for UC Davis single-center trials**

Investigators are required to report **Serious Adverse Events** as well as other **unanticipated problems** to the IRB within five days of the investigator becoming aware of such an event, provided that all four of the following criteria are met:

The event or problem:

1) Occurred at UC Davis; and

2) Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized; and

3) Is unanticipated; and
4) Is related or possibly related to the research: an adverse event is “related to the research procedures” if in the opinion of the principal investigator, it was more likely than not to be caused by the research procedures or if it is more likely than not that the event affects the rights and welfare of current participants.

In the Report, the Investigator will either justify why no changes to the protocol or consent form are needed or attach proposed modifications to the report. The Investigator must respond to all requests from the IRB for further information within 10 working days of receipt of the request. Failure to respond may result in suspension of the study until the issue is resolved.

**Reporting for Multicenter Clinical Trials**

Serious, unanticipated, and related or possibly related events occurring on multicenter trials are to be reported to the IRB within five days of the investigator becoming aware of such an event. These events are defined as serious adverse events experienced by subjects enrolled at other institutions engaged in the same clinical trial as the trial at UCD. Typically, investigators at all participating institutions learn of such events via reports that are distributed by the sponsor or coordinating center of the multicenter clinical trial.

Examples of other problems to be reported:

- An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
- Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
- A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- A breach of confidentiality.
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Change to the protocol made without prior IRB review to eliminate an apparent immediate hazard to a research participant.
- Incarceration of a participant in a protocol not approved to enroll prisoners.
- Sponsor imposed study suspension for risk.
- Adverse emotional reactions to study procedures, such as depression or threat of harm to self or others, or that require medical, psychological or legal intervention to prevent such outcomes.
- Unanticipated medical/physical reactions or injuries temporally related to a study.
• A lab reports blood studies performed the previous week were in error.
• Unanticipated identification of incidences of child abuse, threats of harm, sexual harassment or other reportable events.
• An investigator loses a laptop that contains confidential information about study participants.

For a list of other reportable examples, please see IRB SOP# 36, Reporting Adverse Events47.

Safety Reporting to the FDA
An IND Safety Report is expedited, written notification to the FDA of an adverse experience associated with the use of a study drug that is both serious and unexpected. Sponsor-investigators need to comply with both the adverse event reporting requirements of the ‘Sponsor’ and the requirements of the ‘Investigator.’ For filing format and requirements, see http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/step7.html.

When to file:
1) For any unexpected fatal or life-threatening SAE associated with the use of the drug, the IND Sponsor-Investigator notifies the FDA of the SAE by telephone or fax as soon as possible, but no later than seven calendar days after initial receipt of the SAE. Then the investigator follows with the written report no later than 15 days after the occurrence.
2) For serious and unexpected, but non-fatal adverse events, file as soon as possible and no later than 15 days after you receive the information of the respective adverse event information or laboratory animal data.

Protocol Deviations Reporting
All protocol deviations from an IRB approved study must be avoided, except to eliminate an immediate hazard to research subjects. All deviations must be reported to the UC Davis IRB in accordance with the IRB SOP #3748.

Definitions
A protocol deviation is any departure or discrepancy between the IRB approved protocol and the actual research activities being performed.

47 http://research.ucdavis.edu_gtirb-sop
48 http://research.ucdavis.edu_gtirb-sop
Substantive Action

A substantive action is one that is required to prevent an adverse event or psychological risk or outcome that requires follow up treatment or monitoring and that is greater than minimal risk.

Types of deviations

A *minor protocol deviation* is a deviation that has no substantive effect on the risks to research subjects and has no substantive effect on the value of the data collected. Deviations that did not result from willful or knowing misconduct on the part of the investigator(s) or research staff; and did not result in or require any substantive action to be taken or result in any change to the subject’s condition or status are considered minor. Investigators are required to report minor deviations to the IRB at the time of *continuing review*, in a tabulated format. The form (Deviations Table) can be found at the IRB website[^49]. It is used to identify and report all minor and major deviations that occurred during the current approval period.

A *major protocol deviation* is a deviation that resulted in or required a substantive action to be taken or resulted in a change to the subject’s condition or status. Deviations that harmed or posed a significant risk of substantive harm to the research participants or damaged the scientific integrity of the data collected for the study, or are evidence of willful or knowing misconduct on the part of the investigator(s) or research staff, or involve serious or continuing noncompliance with federal, state, or local research regulations are considered major. Investigators are required to report major deviations to the IRB within 5 *working days* by completing the major deviations protocol form.

Continuing Review Report/ Progress Report

IRBs are responsible for continuing review of ongoing research to ensure that the rights and welfare of human subjects are protected. FDA regulations regarding continuing review require an IRB to develop and follow written procedures for:

- Conducting continuing review of research at intervals appropriate to the degree of risk, but not less than once per year [21CFR 56.108(a)(2)]
- Determining which studies need verification from sources other than the investigator that no material changes in the research have occurred since the previous IRB review [21CFR 56.108(a)(2)]
- Ensuring that changes in approved research are promptly reported to, and approved by, the IRB [21CFR 56.108(a)(3-4)]

• Suspending or terminating approval of research that is not being conducted in accordance with the IRB’s requirements [21CFR 56.108(b)(s) and 56.113]

**Criteria for Conducting Continuing Review**

The following criteria are the same for initial review and continuing review and include a determination by the IRB that:

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Informed consent is adequate and appropriately documented
- Where appropriate, the research plan makes adequate provision for monitoring the data to ensure the safety of subjects
- There are adequate provisions to protect the privacy of subjects and to maintain confidentiality of data
- Appropriate safeguards have been included to protect vulnerable subjects

At the time of Continuing Review, all adverse events, which meet the reporting criteria, are required to be reported in a tabular format as part of the progress report. In addition, all UC Davis events which were classified as “mild” or “moderate” are to be reported in this same tabular format. The report should be limited to events which occurred since the last reporting period. The Progress Report Form is completed with the renewal notice and needs to include all relevant documentation for review. The Request for Permanent Closure of all Study Activities form is to be completed at the end of the study. The Guidance and forms are available at the IRB website at [http://research.ucdavis.edu/gt/irb-sop](http://research.ucdavis.edu/gt/irb-sop).

**FDA Annual Reports**

Annual reports must be submitted within 60 days of the anniversary date that the IND went into effect. Required content is listed in 21CFR 312.33. For more details, see [http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/step8.html](http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/step8.html).
Monitoring/Auditing/Inspections

- Monitoring
  Monitoring is the act of **overseeing the progress** of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCPs, and the applicable regulatory requirement(s).

- Auditing
  An audit is a **systematic and independent examination** of trial-related activities and documents to evaluate whether the trial-related activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, sponsor’s SOP, GCP, and other applicable regulatory requirements. Auditors collect evidence and compare against standards, review documents, assess deviation and non-compliance and recommend actions.

- Inspections
  For detailed description of quality systems, please see ICH GCP Guidelines E6 (Step 5).

FDA inspections

The Bioresearch Monitoring Unit of the FDA may conduct inspections of medical research and testing facilities in order to ensure studies avoid bias and follow proper testing procedures. The FDA inspector will review all case study data and may interview subjects and doctors. In all types of inspections, an FDA inspector checks the study for errors that affect the outcome.

At UC Davis, we may expect the following types of inspections:

- **Routine Inspection** may be conducted at random. It is sometimes triggered by abnormally high enrollment rate as well as large studies to promote a pivotal drug.

- **For-Cause Inspection** FDA investigator has a reason to check out a research facility i.e., subject complaint, a highly publicized drug, unqualified investigators, large AE clustering.

Once you receive notification of the FDA audit notify the UCDHS Compliance Office at 916-734-8808. Specific procedures to follow when preparing for an inspection and on the day of the inspection are outlined in the P&P 1506.50

CTSC Quality Assurance Program (Clinical Trials Group)

CTSC Quality Assurance Program is comprised of both auditing and monitoring elements implemented as needed based on the scope of the clinical research project. The program is offered to all investigator-initiated studies that otherwise are not audited/monitored by another entity. The program aims to provide a proactive (as opposed to “for cause”) regulatory assessment of the studies in order to preclude the development of non-compliance situations. The program is provided at no cost for unfunded studies. The recharge rate for funded studies are negotiated on an individual basis.

A written report is submitted to the investigator after each trial QA visit. The report contains the date of the visit, a summary of what was reviewed and statements concerning the significant findings, deviations, deficiencies, conclusions, actions taken (or to be taken) and/or recommendations to secure compliance.

When writing a grant proposal consider including costs for monitoring of the study, as these costs could be quite substantial. Contact the CTSC Clinical Trials Resource Group for the details.

UC Davis IRB Audits (Quality Improvement Program)

The IRB Administration has developed a Quality Improvement Program (IRB SOP #50^51) to improve human research protections at UC Davis. The mission of the program is to heighten investigator and IRB awareness of regulatory requirements and improve the ethical conduct of research. The primary quality improvement activity is the audit of investigator research records and the corresponding IRB files. Examples of quality improvement audits include, but are not limited to:

- For-cause audits
- Audits triggered by complaints from research participants or others
- Random audits of:
  - high-risk studies
  - studies involving vulnerable subjects
  - FDA regulated studies
  - studies recently audited by an external sponsor
  - studies audited by internal offices (UC Davis/UCDMC, etc.)
  - protocols chosen randomly.

In cases of non-compliance, the IRB has the authority to suspend the research, requests modifications, or terminate the study (see IRB SOPs #51 (Investigating Non-Compliance), #52 (Suspension or Termination of IRB Approval))^52.

51  http://research.ucdavis.edu/gt/d/irb/
52  http://research.ucdavis.edu/gt/d/irb/
Monitoring Visits

Monitoring is the act of **overseeing the progress** of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCPs, and the applicable regulatory requirement(s).

The sponsor-investigator, sponsor or contract research organization (CRO) acting on behalf of the pharmaceutical company sponsor is responsible for assuring that the data collected throughout the study are accurate. A monitor is assigned to the study site to oversee the progress of a clinical trial. During a monitoring visit, individual subject records and source documents, Regulatory Binder and other essential documents are reviewed and compared to data recorded on the case report forms (CRF) to ensure the following:

- Subjects meet eligibility requirements.
- The rights and safety of human subjects are protected.
- Informed consent has been obtained and documented appropriately.
- Conduct of trial is in compliance with protocol, good clinical practice (GCP), and applicable regulatory requirements.
- Subject was followed and treated according to the protocol.
- Reported trial data are accurate, complete, and 100% verifiable from source documents. All pertinent information in the subject records was accurately recorded on the CRF.
- The CRF is complete, legible, and consistent throughout visits.

Inconsistent or unclear entries will need to be corrected by the investigator or staff. The Principal Investigator and Research Coordinator should be available during the monitoring visit to address any questions, queries and to make necessary corrections.

Financial Steps Post-IRB Approval

**Scheduling and Registration of outpatient study subjects**

In order to efficiently separate charges to bulk account vs. insurance account, the UCDHS created a new financial class for **outpatient** study patients. These research accounts (47-accounts53) are used to place study charges that go to the bulk accounts. Study charges placed on 47-accounts are never billed to the patient. A 47-account type is opened in the Invision Scheduling and Registration System. This account type is linked with the bulk account number, which is entered in place of insurance charges.

53 [http://intranet.ucdmc.ucdavis.edu/researchbudgeting/#47accounts](http://intranet.ucdmc.ucdavis.edu/researchbudgeting/#47accounts)
information. In addition, hospital code RSH (Research) and plan code 121 are added to the account. All together, these components enable the seamless routing of the charges placed on this account type to the bulk account for the study. A coordinator or a MOSC can open the 47-accounts.

Refer to your Coverage Analysis to determine if you have hospital/clinic charges payable by your study bulk account.

A 47-account is only required if the research procedures are billed through the UCDHS billing system (e.g. laboratory and radiology services). In cases where the entire study is billed to Medicare or to private insurance, procedures are billed via the patient’s regular insurance accounts (38- or 40- accounts). In this case, no billing to the bulk account occurs, and therefore 47-accounts are not required.

Once the 47-account type is opened for the research patient, the outpatient visit can be scheduled using this account. In some instances it makes sense to perform both types of care (research-related and non research-related care) during a single visit. Such situations necessitate two separate scheduling events, on a patient 38-account (or other appropriate standard care account type) and a 47-account. These events could be scheduled only 1 min apart in Invision. Once the patient is scheduled on a 47-account, this action translates in the EMR as a separate scheduling line, titled “Research.” Scheduling the same patient on two types of accounts, results in two separate encounters in EMR (e.g. “Office visit” and “Research”). The physician must choose the appropriate encounter to place the orders and make notations. Services billed to patient insurance are documented on the routine services encounter, and services billed to the bulk account are placed on the “Research” encounter.

47-type accounts will remain open for 999 days, unless explicitly closed by the research team. For detailed information on 47-accounts, see: http://intranet.ucdmc.ucdavis.edu/researchbudgeting/#47accounts.

Scheduling and registration of inpatient, emergency and short stay patients

These type of patients do not have alternative accounts. They are admitted using the usual admission process. In order to correctly separate the charges, the UCDHS utilizes the “Bill Hold” process. This means that the bills for those patients that have study-related charges that are payable by study accounts and by insurance are stopped. Next, an itemized listing of services has to be reviewed by a CRC or PI, and the charges manually classified as “insurance” or “bulk.” The Bill Hold process is enabled by modifications of Invision Admission records to include plan codes 121 and 136. For specific steps please refer to CTSC Clinical Research SOP #10A54.

54 http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml
Billing Reconciliation

The principal investigator or CRC should review the research bulk accounts on a monthly basis to ensure that all charges are appropriate and no charges are missing or duplicated. Research billing corrections may also be required as a result of a research billing review conducted by Compliance. If you identify an incorrect charge, refer to CTSC Clinical Research SOP 11 for detailed information on how to correct the charges.

Invoicing

Hospital Policies and Procedures P&P 1802 and P&P 1816 require that all departments prepare a DaFIS Accounts Receivable invoice to bill sponsors for amounts due to the University for services rendered and a separation of duties is required to prepare, track and reconcile invoices.

Since each clinical trial contract has unique terms and payment schedule, a separate accounts receivable file for each contract should be established to house data for invoice preparation. A tracking form should be kept current for each trial participant. This form will track the study visits/dates and any additional “invoicable” procedures that were performed. This data should be verified against study enrollment and screening logs to ensure that all participants are included on an invoice. The tracking forms are used as supporting documentation to prepare an invoice. The invoice is entered into the DaFIS system and sent to the sponsor for payment. The invoice is prepared and formatted in accordance with payment terms outlined in the contract and is sent to the sponsor.

Research payments should be directed to the CRC and reconciled against outstanding invoices. The coordinator will cite the study’s DaFIS account number on the payment and forward to the department to credit to the correct account. If needed, the coordinator should request from the sponsor a detailed breakdown of the payment.
Step 1. Track the study visits:

**XXX PATIENT ENROLLMENT LOG**

<table>
<thead>
<tr>
<th>Screen #</th>
<th>Patient Initials</th>
<th>Date Consent Signed</th>
</tr>
</thead>
<tbody>
<tr>
<td>00001</td>
<td>ABC</td>
<td>6-Jun-11</td>
</tr>
<tr>
<td>00002</td>
<td>ECU</td>
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</tr>
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<td>00003</td>
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</tr>
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<td>00004</td>
<td>NKP</td>
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</tr>
<tr>
<td>00005</td>
<td>QMS</td>
<td>4-Aug-11</td>
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<tr>
<td>00006</td>
<td>TUV</td>
<td>2-Sep-11</td>
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<tr>
<td>00007</td>
<td>WXY</td>
<td>2-Sep-11</td>
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<tr>
<td>00008</td>
<td>BDO</td>
<td>8-Sep-11</td>
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<tr>
<td>00009</td>
<td>GHI</td>
<td>15-Sep-11</td>
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<tr>
<td>00010</td>
<td>JKL</td>
<td>28-Sep-11</td>
</tr>
<tr>
<td>00011</td>
<td>NNO</td>
<td>7-Oct-11</td>
</tr>
<tr>
<td>00012</td>
<td>PQR</td>
<td>7-Oct-11</td>
</tr>
<tr>
<td>00013</td>
<td>ZYX</td>
<td>4-Jan-12</td>
</tr>
</tbody>
</table>

**TREATMENT PERIOD PLACEDO AND STUDY MEDICATION**

<table>
<thead>
<tr>
<th>Screen #</th>
<th>Patient Initials</th>
<th>Date Consent Signed</th>
<th>Run-In</th>
<th>Blinding</th>
<th>Double-blind Period</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>00001</td>
<td>ABC</td>
<td>6-Jun-11</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</tr>
<tr>
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<td>2</td>
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</tr>
<tr>
<td>00004</td>
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</tr>
<tr>
<td>00005</td>
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<td>4-Aug-11</td>
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<td>2</td>
<td>3</td>
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</tr>
<tr>
<td>00006</td>
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<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
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<td>WXY</td>
<td>2-Sep-11</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</tr>
<tr>
<td>00008</td>
<td>BDO</td>
<td>8-Sep-11</td>
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<td>2</td>
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</tr>
<tr>
<td>00009</td>
<td>GHI</td>
<td>15-Sep-11</td>
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<td>2</td>
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<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Step 2. Generate Invoice based on the completed study visits.

**TREATMENT PERIOD PLACEDO AND STUDY MEDICATION**

<table>
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<tr>
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</tr>
</tbody>
</table>

**Important role of V70.7 Diagnosis Code**

The V70.7 diagnosis code plays an important role when billing Medicare for research procedures. “V70.7” placed in different positions on a bill identifies a patient’s participation in a clinical trial and fulfills the requirements for diagnosis reporting based on Medicare rules. This code also helps UCDHS Health Information Management to separate research-related procedures and visits from routine care visits for legal purposes.

Even if the research participant is undergoing Standard of Care routine procedures, the diagnosis code V70.7 must be documented and reported along with the patient’s primary diagnosis.
UCDHS Policy and Procedure P&P 2317 requires that V70.7 is added to the problem list for all subjects participating in drug and device studies. Moreover, any orders for these research patients should be associated with V70.7.

Placing Radiology and Laboratory Orders for Research Patients

The orders for Lab or Radiology services ordered in EMR using a regular OFFICE visit, and scheduled on either 38- or 40- account, should be associated with a PRIMARY diagnosis and a SECONDARY diagnosis of V70.7. The bills for these research participants will be reported to Medicare (with the V70.7 in the secondary position) in accordance with the Medicare requirements. The Radiology Department must have the signed Procedure Request Form on file in order to complete the study visit and correctly bill the bulk account. For a detailed process map for radiology services, see: http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml.

Lab or Radiology services ordered in EMR using a RESEARCH visit (and scheduled on a 47- account) should be associated with the V70.7 diagnosis code only. Simply placing the order on a 47-case is not sufficient to complete the lab visit. Phlebotomists at the draw station are not always able to link the order with the account number. Therefore, to ensure that your order is correctly billed to the bulk account, this order must be printed. The printed order should accompany the patient or the sample to the Lab. For detailed process map for lab orders see: http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml.

Study Closeout

At the end of a study, regulatory and financial documentation has to be completed. Closure notices must be sent to Finance to close the Bulk Account and DaFIS (Koali) account. Investigational Drug Service (IDS), IRB and UCDHS Contracts should be notified. A brief study close-out summary follows:

- All CRFs and data have been submitted
- All study drugs have been accounted for and returned, IDS is notified
- UCDHS Contracts is notified
- Final review notification has been sent to the IRB
- All study documentation is present and complete
- Record retention was discussed with the PI
- Bulk account and DaFIS accounts closed
- Accounts Receivable are reconciled with the patient visits
- Final invoice is sent to sponsor

57  http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml
58  http://intranet.ucdmc.ucdavis.edu/researchbudgeting/#47accounts
Management of investigational drugs

Investigational Drug Service (IDS)

According to 21 CFR 312.62(a), an investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. At UCDHS all investigational drugs or biologics (also known as “test articles”) are distributed by the Investigational Drug Services (IDS), a Division of the Pharmacy Department59.

IDS Charges

IDS charges start up fees (non-refundable, one time set-up charge) and dispensing fees. Please see IDS website (http://www.ucdmc.ucdavis.edu/clinicaltrials/IDS/ids.html) for calculation of charges.

IDS Functions

IDS stores and dispenses drugs in accordance with Good Clinical Practice Guidelines, the study protocol requirements, and all applicable rules and regulations. IDS is responsible for:

- Establishment of Standard Operating Procedures (SOP) for each study
  - a copy for Sponsor
  - a copy for Investigator’s file
- Proper storage conditions
  - Temperature logs
  - Documentation of excursions
- Segregation of study agents by protocol
- Isolation of expired and damaged study agents

IDS maintains an inventory of each investigational drug stored in the pharmacy. This record (Drug Accountability Form or DARF) contains:

- Drug’s name, dosage form, strength, lot number and expiration date.
- Dispensing Information:
  - Date
  - Subject info (ID, initials, etc)
  - Dose
  - Quantity dispensed/received/wasted
  - Balances
  - Signature/initials

IDS also maintains randomization codes of patients receiving the drug. As a rule, treatment should not be unblinded except under emergency conditions, which are typically described in the protocol. Before unblinding, the process should be discussed with the study sponsor.

At the conclusion of the study, the pharmacist returns, transfers or disposes of all unused investigational drugs according to the specific instructions provided by the sponsor or sponsor-investigator.

**Overview of Investigational Drug Management process at UCDHS:**
Prescribing and Dispensing of Investigational Drugs and Biologics

Prior to the pharmacy dispensing properly prepared study medication(s), they must verify that:

- The subject has signed the informed consent document
- The study protocol is available in the pharmacy
- The protocol is currently approved by the IRB
- Drug information is available in the pharmacy
- There is a valid and complete physician’s order for the investigational agent.
- The prescription label for an investigational drug will be marked “For Investigational Use Only”

Only the PI and sub-investigators listed on the FDA Form 1572 may write orders for study agents, except for:

- “Authorized Prescribers List”
- Clinicians on “IRB Research Personnel List”

The prescription must contain ALL information currently required by state, federal and institutional laws and policies, including: name & address of patient; name & quantity of drug; date of issue; typed or printed name, address and phone# of prescriber; signature of prescriber.

IDS follows written sponsor instruction for disposal/destruction documented in the Investigational Agent Disposition Record.

Dietary Supplements

IDS may administer dietary supplements if the research involves the use of a supplement to treat a disease (intended for use in diagnoses, cure, relief, treatment, or prevention of disease or intended to affect the structure or function of the body), or involves significant risk to subjects. If any of the above criteria are met, the FDA requires submission of an IND (Investigational New Drug) Application. For studies under INDs, the supplement is treated as investigational drug.

IDS Contact:

2315 Stockton Blvd, Rm DT 0762, Sacramento, CA 95817
Phone: (916) 703-4093
Pager: (916) 762-3929
Email: IDS@ucdmc.ucdavis.edu
Study Documents

Source Document Binder

Per ICH GCP guideline E6 section 1.51 source data is defined as “all information in original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.” This is the first recording of subject-related information. According to 21 CFR 312.62(b), an investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual. Source documents must be complete, accurate, and valid. The regulatory authorities consider source documents to be the basis for all trial data and the adjudication of the outcome of events.

The purpose of source documents/patient record chart:

- To document the existence of the participant and substantiate integrity of trial data collected.
- To include original documents related to the trial, medical treatment, history of participant, and participant’s condition while on-study or in follow-up.
- To provide an auditable link in the chain from the study database back to the original source (visit worksheet)
- Collect data for transfer to CRFs and then to the study database.
- To instruct study coordinators and other site personnel on what data to collect and information necessary to answer data queries.
- Can be electronic media, original documents or certified copies
The following Source Documents should be filed in the Source Document Binder.

<table>
<thead>
<tr>
<th>Document</th>
<th>Requirement/Purpose</th>
<th>File</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital, clinic, office records, Progress notes, medical history, Subject diaries, study questionnaires</td>
<td>1) To document the existence of the subject and substantiate integrity of trial data collected. 2) To include original documents related to the trial, medical treatment, history of subject, and subject’s condition while on-study or in follow-up. Electronic media, original documents or certified copies.</td>
<td>Source Document Binder</td>
<td>• 21CFR11  • 21CFR312/812  • FDA Guidance: E6 GCP, Sections 1.51, 1.52, 5.20, 8.3.13</td>
</tr>
<tr>
<td>Inclusion/Exclusion Checklist, Study visit Evaluation checklist</td>
<td>To document subject eligibility in the study. First recording of study specific visits and procedures</td>
<td>Source document Binder</td>
<td></td>
</tr>
<tr>
<td>Signed informed consent including Assent, HIPPA, Subject Bill of Rights</td>
<td>1) Written informed consent form to document that consent is:  • Obtained in accordance with regulations, GCP, and protocol.  • Dated prior to participation of each subject in trial. Provided for direct access to records.</td>
<td>Source Document Binder</td>
<td>OHRP Informed Consent Guidance Information</td>
</tr>
<tr>
<td>Note to File (Memos), Correspondence (subject related)</td>
<td>Study related NTF on subject participant Documentation of phone contact, email or mail</td>
<td>Source Document Binder</td>
<td></td>
</tr>
<tr>
<td>Laboratory report/x-ray reports/ECG report</td>
<td>Subject’s study related lab or x-ray reports while active in the study.</td>
<td>Source Document Binder</td>
<td></td>
</tr>
<tr>
<td>Concomitant medication list, adverse event, SAE, Procedure form</td>
<td>Document subject’s concomitant medication before and during the trial, any adverse event, surgical/treatment procedures or serious adverse event</td>
<td>Source Document Binder</td>
<td></td>
</tr>
</tbody>
</table>
Case Report Forms (CRF) Binder / Electronic Case Report Form (eCRF)

According to ICH GCP E6 1.11, a case report form is a printed, optical, or electronic document designed to record all of the protocol required information to be reported on each trial subject. CRFs are designed by the sponsor or sponsor-investigator and maintained at the investigative site. Information documented on the CRF must be supported by a source document. CRFs should record that:

- Study subjects met the eligibility criteria (inclusion/exclusion)
- Protocol-specified clinical laboratory testing (including EKGs, X-rays, eye exams, etc) was documented by laboratory records
- All AEs were documented and appropriately reported
- Clinical investigator assessed severity of AEs and documented relationship of event to test article, (including any AE that was previously anticipated and documented by written information from the sponsor)
- All concomitant therapies and/or inter-current illnesses were documented and reported
- Report of all dropouts and the reasons

One of the most essential tasks performed by the CRC is to complete and/or ensure the completion of the subject’s CRF. Most sponsors will provide instructions or a guide for CRF completion. Handwriting must be legible and should be completed in black ink. All data points must be addressed and for fields that can not be completed, “not available,” “not done,” or “unknown” should be marked in accordance with the sponsor’s instructions.

The CRC will ensure that all required data are collected and entered on the CRF as soon as possible after, if not during, the visit. All CRFs should be checked for completeness and legibility. The CRFs should be reviewed and signed by the investigator prior to submission. Only those physicians identified on the 1572 may sign CRFs.

When making a correction on a CRF, a single line should be drawn through the incorrect entry and the correct data should be entered above or next to the incorrect entry, leaving the original data legible. The correction should be dated and initialed. White-out, obliterating or erasing should never be used to correct an error. Blanks identified prior to the investigator’s review and sign-off on the CRF can simply be completed. Those identified after sign-off must be dated and initialed. See Appendix 5 for an example.
<table>
<thead>
<tr>
<th>Document</th>
<th>Requirement/Purpose</th>
<th>File</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Case Report Forms | 1. Dated, completed case report forms (CRFs):  
• To document that the investigator or authorized member of the investigator’s staff confirms the observations recorded.  
• To document all changes/additions or corrections made to CRFs after initial data were recorded.  
• Signed if required by Group SOPs or if used as source documentation.  
2. Originals retained by sponsor after study completion and/or site closure.  
3. Site retains copy.                                                                 | File (CD for eCRF) in regulatory binder                                                                 | • 21CFR312/812  
• FDA Guidance: E6 Good Clinical Practice (GCP), Sections 1.11, 4.9, 5.5, 5.23, 8.3.14, 8.3.15 |

**Study Financial Binder**

Per CTSC SOP #5, 6, 8, UC Davis requires that a study financial binder be prepared and kept on file with all of the financial documentation for the trial. As of 12/2010, the following documents are mandatory for each clinical trial, and should be kept in the Study Financial Binder (or in the electronic format).

1. Coverage Analysis (consists of Qualifying Clinical Trial form and Billing Grid)  
2. Internal Budget prepared in the Unified Budget Template  
3. Feasibility assessment (a document outlining the scientific value of the trial and assessing the feasibility of the performance)

Per SOP #11, the clinical research team is required to file the monthly billing statements and demonstrate reconciliation of billing statements with the Billing Grid.
The following is an outline of the documents that should be kept in the financial binder:

<table>
<thead>
<tr>
<th>Document</th>
<th>Requirement/Purpose</th>
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<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage Analysis</td>
<td>Coverage Analysis is a document that outlines what hospital procedures may be paid by Medicare/Insurance, and what procedures must be paid by the study budgets. Consists of two parts: Qualifying Clinical Trial form and Billing Grid</td>
<td>Financial Binder</td>
<td>CTSC SOP #4</td>
</tr>
<tr>
<td>Internal Budget</td>
<td>Internal Budgets for all clinical trials are based on the coverage analysis and on the contract (if applicable)</td>
<td>Financial Binder</td>
<td>CTSC SOP #8</td>
</tr>
<tr>
<td>Feasibility Assessment</td>
<td>Outlines the scientific importance for the study and balances it with probability of accrual and financial solvency</td>
<td>Financial Binder</td>
<td>CTSC SOPs #5,6</td>
</tr>
<tr>
<td>Billing Statements</td>
<td>Monthly billing statements are provided to every Coordinator</td>
<td>Financial Binder</td>
<td></td>
</tr>
<tr>
<td>Billing Grid for each patient</td>
<td>Enables tracking of each patient events throughout the life of the trial</td>
<td>Financial Binder</td>
<td></td>
</tr>
<tr>
<td>Signed Agreements</td>
<td>To document agreements between involved parties, if any. These must be signed by an individual authorized by the institution to sign on behalf of The Regents of the University of California. This includes Confidential Disclosure Agreements (CDAs), Nondisclosure Agreements (NDA), Material Transfer Agreements (MTAs) and Clinical Trial Agreements (CTAs). For example: • Investigator/institution and sponsor (e.g., contracts, grants) • Investigator/institution and affiliated sites (e.g., contracts) • Investigator/institution and authorities (where required)</td>
<td>Financial Binder</td>
<td>• 21CFR312 /812  • FDA Guidance: E6 GCP, Sections 4.9.6, 5.6, 8.2.6</td>
</tr>
<tr>
<td>Subject Identification Code List</td>
<td>1. To document that the investigator keeps a confidential list of names of all subjects allocated to trial numbers upon enrolling in the trial. 2. Allows investigator/institution to permit identification of all subjects enrolled in the trial in case follow-up is required. 3. List needs to be kept in a confidential manner.</td>
<td>Also in Regulatory Binder(file at the end of study) File in study financial binder during the study.</td>
<td>• FDA Guidance: E6 GCP, Sections 1.58, 8.3.21, 8.4.3</td>
</tr>
</tbody>
</table>
Regulatory Binder (Essential Documents)

Essential documents are those documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements (ICH Guideline E6).

At UC Davis, the following list represents the required essential documents that must be filed in the regulatory binder. All essential documents must be available for audit/inspection by the sponsor and regulatory authorities.

<table>
<thead>
<tr>
<th>Document</th>
<th>Requirement / Purpose</th>
<th>File</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Assent Form</td>
<td>• Assent of children and permission of parents or legal guardians as determined by the IRB/IEC is required as per the provisions of 45CFR46.</td>
<td>Regulatory binder</td>
<td>• 45CFR46, Subpart D</td>
</tr>
<tr>
<td></td>
<td>• State law where the research is taking place defines the age of a minor and requirements for emancipation.</td>
<td></td>
<td>• 21CFR50</td>
</tr>
<tr>
<td></td>
<td>• The Assent Form is used for children ages 12-17.</td>
<td></td>
<td>• 21CFR56</td>
</tr>
<tr>
<td></td>
<td>• The requirement for assent of children and/or permission of their parents or legal guardians may be waived by the IRB as long as the criteria for waiving consent in the regulations (45CFR46) are met.</td>
<td></td>
<td>• FDA Information Sheets, Guidance for IRBs and Investigators 1998</td>
</tr>
<tr>
<td></td>
<td>• Keep on file all versions submitted and approved by the IRB.</td>
<td></td>
<td>Update, FAQ Nos. 47 and 48; and Page 5</td>
</tr>
<tr>
<td>Assurance</td>
<td>• The Institution is responsible for obtaining and maintaining a current Health &amp; Human Services (HHS) Assurance through the Office of Human Research Protection (OHRP).</td>
<td>Regulatory binder</td>
<td>• 45CFR46</td>
</tr>
<tr>
<td>Number</td>
<td>• The principal investigator (PI) is responsible for ensuring that a current Assurance is in effect while conducting research on human subjects in HHS funded studies.</td>
<td></td>
<td>• OHRP Procedures for Registering IRBs and Filing Federal Wide Assurances of Protection for Human Subjects (FWA)</td>
</tr>
<tr>
<td></td>
<td>• All performance sites:</td>
<td></td>
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<td></td>
<td>• Main site</td>
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<td></td>
<td>• All affiliated sites that meet the OHRP requirements for having an Assurance.</td>
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<tr>
<td></td>
<td>• Must be renewed prior to expiration.</td>
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<tr>
<td></td>
<td>• Keep on file the Assurance number and expiration date.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Document</td>
<td>Requirement / Purpose</td>
<td>File</td>
<td>Reference</td>
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</tbody>
</table>
| **Communications/Correspondence** | 1. All relevant communications, other than site visits, to document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting, etc. For example:  
• Letters  
• Meeting notes  
• Notes of telephone calls  
• Email messages  
2. Includes communications to and from the Sponsor and/or the protocol team.  
3. Communications about a specific subject must be filed with source documents in the subject's research record.  
4. Save electronic media, originals, and/or certified copies. | Regulatory binder | • ICH Guidance: E6 GCP, Sections 4.4, 4.9, 8.3.11 |
| **Curriculum Vitae (CV) Medical License, DEA License (if applicable)** | 1. The site must have on file CVs and/or other relevant documents evidencing qualifications and eligibility to conduct the trial and/or provide medical supervision of subjects. Includes the following key personnel:  
• Principal investigator (i.e., individual responsible for the grant/contract at the site).  
• Investigator responsible for day-to-day activities of the site.  
• For IND studies: Investigator of Record (IOR)  
All other investigators/ subinvestigators and any other clinicians listed on a Form FDA 1572, Box # 6.  
• For non-IND studies, all other investigators/ subinvestigators and any other clinicians listed on an authorized prescribers list.  
• Study coordinator  
• Pharmacist of record  
2. Update to reflect significant changes:  
• Affiliation  
• Education  
• Responsibilities | Regulatory binder | • 21CFR312/812  
• ICH Guidance: E6 GCP, Sections 4.1, 4.3, 5.6, 8.2.10, 8.3.5 |
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| **Final / Close-Out Monitoring Report**  | 1. A close-out report by the monitor to document that all activities required for site close-out are completed and essential documents are in the appropriate files. Includes the following:  
   • Disposition of subjects  
   • Location of research records  
   • Disposition of specimens  
   • Disposition of study drug  
   • IRB notification  
   2. Applies only to sites being closed (i.e., no longer enrolling new subjects or following any subjects on-study). | Regulatory binder | • 21CFR312 /812  
• ICH Guidance: E6 GCP, Sections 4.13, 8.4.5 |
| **Final Study Report**                  | Final report by the investigator to the IRB, and where applicable, to the regulatory authorities to document completion of the trial. Include the following information:  
   • Disposition of subjects  
   • Location of research records  
   • Disposition of specimens  
   • Disposition of study drug  
   • Other information as required by the IRB (e.g., number of patients screened, number enrolled, serious adverse experiences, etc.). | Regulatory binder | • 21CFR312 /812  
• ICH Guidance: E6 GCP, Sections 4.13, 8.4.7 |
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<td>Financial Disclosure</td>
<td>1. To document financial aspects of the trial and the financial agreement between the investigator / institution and the sponsor for the trial. 2. Certification or Disclosure • Certify that there is no financial interest, or • Disclose specific financial interests. • Must complete Office of Research form 700U and FDA forms 3454 or 3455, or equivalent forms. 3. Applies to investigators and subinvestigators 4. Applies to individuals who fit any of the following criteria: • Sign the Form FDA 1572 (Investigator of Record) • Identified as an investigator in initial submissions or protocol amendments under an IND. • Identified as an investigator in the NDA. • For studies not conducted under an IND, the individuals whom the sponsor considers to be investigators and subinvestigators. • Individuals who actually conduct and take responsibility for an investigation. • Individuals who have the ability and opportunity to significantly impact the data as determined by the site. • Spouses and dependent children of individuals indicated above. 5. The IRB may have additional requirements.</td>
<td>Regulatory binder</td>
<td>• 21CFR54 • 42CFR50, Subpart F • 21CFR312/812 • ICH Guidance: E6 GCP, Section 8.2.4 • FDA Guidance: Financial Disclosure by Clinical Investigators • NIH Notice OD-00-040</td>
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| **Form FDA 1572 (Statement of Investigator)** | 1. Required for each initial protocol registration submission of a new protocol with an Investigational New Drug (IND) application (Form FDA 1571) | Regulatory binder | • 21CFR312  
• ICH Guidance: E6 GCP, Sections 4.1, 4.3 |
| | 2. The Investigator listed in Box 1 of the 1572 is the individual who must sign and date the form. This individual is referred to as the Investigator of Record (IOR). | | |
| | 3. Only laboratories not specified in the protocol need to be listed in Section 4. | | |
| | 4. Section 6 must list any individual:  
• Responsible for the medical management of subjects.  
• Authorized to prescribe study medication.  
• This may include, but is not limited to, the following:  
  – MDs  
  – Pharmacists  
  – Nurse Practitioner  
  – Physician’s Assistant  
  – Study Coordinator  
• If there are no individuals that need to be listed, then record “NONE”. | | |
| | 5. Update as study personnel and/or other data on the form change. Updated forms must be signed and dated by the IOR. | | |
| | 6. The original version and any updated forms must be submitted to the sponsor (if applicable) and the FDA. | | |
| | 7. A copy of the forms must be kept on file at the site. | | |
| **IRB Approved Information Given to Study Subject** | 1. To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent. | Regulatory binder | • 45CFR46  
• 21CFR50  
• 21CFR56  
• ICH Guidance: E6 GCP, Sections 4.8, 8.2.3 |
| | 2. To document that recruitment measures are appropriate and not coercive. | | |
| | 3. Include the following:  
• Informed consent form  
• All applicable translations  
• Advertisement for subject recruitment (if used)  
• Education materials (protocol specific)  
• Any other written information  
• Protocol specific diaries and questionnaires | | |
1. Written informed consent form to document that consent is:
   • Obtained in accordance with regulations, GCP, and protocol.
   • Dated prior to participation of each subject in trial.
   • Provided for direct access to records.
2. Non-English speaking subjects must be consented in a language they can understand.
   • Save all written translations.
3. Consents obtained for screening purposes must be retained even if the subject was not enrolled in the protocol.
4. To document revisions of these trial-related documents that take effect during trial, save all versions submitted and approved by site’s IRB:
   • Informed consent form.
   • Any other written information provided to subjects.
5. Continual reviews are at the directive of the IRB.
6. Changes in consent forms due to protocol amendments and important safety information must be submitted and approved by the IRB.

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1. To document that relevant and current scientific information about the investigational drug/agent has been provided to the investigator.
2. Include updates to document that investigator is informed in a timely manner of relevant information as it becomes available.
3. Keep on file a copy for EACH of the study drugs/agents used within the protocol.
4. Include the following:
   • Only the most recent version.
     – All obsolete versions must be removed.
     – Obsolete IBs must be shredded since they may contain proprietary information.
     – Shred upon removal from file, or upon trial completion.
   • Addendum to IBs (e.g., all IND safety reports related to the drug/agent).
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<td>1. Copies of all materials submitted to the IRB, including any local committees as required by the IRB, for example but not limited to: • Cancer Center Scientific Review Committee • Radiation Use Committee • Other Hospital Committees per IRB requirements</td>
<td>Regulatory binder</td>
<td>- 45CFR46</td>
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<td>2. Dated proof of submission and IRB approval of the following for both initial submissions and revisions (if any). Revised documents must be labeled (e.g., date and/or version number) to differentiate them from previous versions. • Advertisements – to document that recruitment measures are appropriate and not coercive. • Continuing/interim review of trial in accordance with federal regulations and IRB policy. • Informed consent form • Protocol • Protocol Amendments and/or Letters of Amendment • Protocol-specific education materials • Subject compensation • Any other documents receiving IRB approval or their favorable opinion. • Any other written information to be provided to subjects, to document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent. • Any other pertinent communications with IRB or documentation required by the IRB. • Clarification memos as required by the IRB.</td>
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<td>- 21CFR50</td>
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<td>3. Dated proof of IRB submission of the following for both initial submissions and revisions (if any). Revised documents must be labeled (e.g., date and/or version number) to differentiate them from previous versions. • IND Safety Reports, Safety Memos, and Safety Alerts (reported with yearly renewal, unless serious, unexpected and related to study, in which case, reported within 5 days of becoming aware of the event.) • Investigator’s Brochures</td>
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<td>- ICH Guidance: E6 GCP, Sections 3, 4.4, 4.5, 4.10, 5.11, 5.17.3, 8.2.3, 8.2.7, 8.3.2, 8.3.3, 8.3.19</td>
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<td>- OHRP IRB Guidebook</td>
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### Document Requirement / Purpose

1. To document competence of local, central, or Group laboratories to perform protocol required tests and support reliability of results of medical/laboratory/standardized procedures/tests, one of the following must be on file:

   **Laboratories located in the United States**
   - CLIA Certification of Compliance
   - CLIA Certification of Accreditation AND the agency certificate (e.g., CAP Certification of Accreditation)

   **Laboratories located outside the United States**
   - Results of established quality control and/or external quality assessment
   - Other validation

2. To document current competency, update files when:
   - Existing certification/accreditation/validation expires.
   - A new laboratory is added or replaces an existing laboratory.

3. Document normal values/ranges for medical/laboratory/standardized procedures/tests included in the protocol.
   - Update when they are revised during the trial.
   - Does not apply to tests that do not have established normal values/ranges.

4. The preceding (1-3) do NOT apply to laboratories that test protocol specimens but do NOT report any subject-specific results for the diagnosis, treatment or assessment of the health of subjects.

### Monitoring Log

Dated signature of monitor for each study visit.

### File Reference

- Regulatory binder
  - 21CFR58
  - 21CFR312
  - 42CFR493.3
  - ICH Guidance: E6 GCP, Sections 4.2, 8.2.11, 8.2.12, 8.3.6, 8.3.7
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| Monitoring Reports | Copies of all site visit reports (hard copy or electronic) to document both the site visits and findings of the monitor.  
*Pre-study visit, Site Initiation visit, Interim Visits and Study Close out Visit. | Regulatory binder     | • 21CFR312/812  
• ICH Guidance: E6 GCP, Sections 1.39, 5.18, 8.3.10                                              |
| Inv Product Accountability Log/Pharmacy Accountability Records | Accountability records must be kept for all study drugs/agents provided as part of the protocol.  
*includes Temperature log | Regulatory binder     | • 21CFR312/812  
• ICH Guidance: E6 GCP, Sections 4.6, 5.13, 5.14, 8.2.15, 8.3.8, 8.3.23, 8.4.1                  |
| Protocol | To document investigator and sponsor agreement to the protocol, amendments and CRFs; and, to document revisions of trial-related documents that take effect during trial:  
• Initial version that the site was registered  
• Amendments and Letters of Amendment  
• Subsequent versions  
• Investigator signature page | Regulatory binder     | • 21CFR312/812  
• ICH Guidance: E6 GCP, Sections 1.44, 1.45, 4.5, 5.23, 6, 8.2.2, 8.3.2                      |
| Protocol Training (Training Log) | Documentation that trial procedures were reviewed with the investigator and investigator’s trial staff:  
• Summary of start-up calls  
• Training meetings (Initiation, Implementation, Investigator Meeting, Teleconference) | Regulatory binder     | • 21CFR312/812  
• ICH Guidance: E6 GCP, Sections 4.5, 5.23, 8.2.20                                              |
| Record of Retained Body Fluids and/or Tissue Samples | If any blood specimens, other body fluids and/or tissue samples are retained for long-term storage at the site, document location and identification of the retained samples. (e.g., A laboratory data management or tracking system.) | Regulatory binder     | • ICH Guidance: E6 GCP, Section 8.3.25  
OHRP Guidance: Issues to Consider in the Research Use of Stored Data or Tissues             |
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| **Screening and Enrollment / Randomization Logs** | 1. To document identification of subjects who entered pretrial screening.  
2. To document chronological enrollment of subjects by trial number  
3. Screening and enrollment/randomization logs may be separate or combined.  
4. Include the following information:  
• Initials of all patients screened for each study  
• Study ID if patient receives one  
• Date screened  
• Date randomized  
  – If not randomized, indicate reason | Regulatory binder | • 21CFR312 /812  
• ICH Guidance: E6 GCP, Sections 8.3.20, 8.3.22 |
| **Subject Identification Code List** | 1. To document that the investigator keeps a confidential list of names of all subjects allocated to trial numbers upon enrolling in the trial.  
2. Allows investigator/institution to permit identification of all subjects enrolled in the trial in case follow-up is required.  
3. List needs to be kept in a confidential manner. | Regulatory Binder(file at the end of study)  
Also file in study financial binder during the study. | • ICH Guidance: E6 GCP, Sections 1.58, 8.3.21, 8.4.3 |
| **Serious Adverse Events (SAE) and Safety Reports** | 1. Notification by originating investigator to sponsor of serious adverse events, related reports, and other safety information.  
2. Notification by sponsor to investigators of safety information.  
3. Where applicable, notification by sponsor or investigator to regulatory authorities and the IRB:  
  • Unexpected, serious and related adverse drug reactions (within 5 days)  
  • Other safety information (at yearly review) | Regulatory Binder | • 45CFR46  
• 21CFR50  
• 21CFR56  
• 21CFR312  
• ICH Guidance: E6 GCP, Sections 1.1, 1.2, 1.50, 1.60, 4.11, 5.16, 5.17, 8.3.16, 8.3.17, 8.3.18 |
### Delegation Log/Signature Log

1. To document the signatures of individuals using initials in place of a full signature to sign CRFs and source documents.
2. To document the signatures and initials of all persons authorized to make entries and/or corrections on CRFs. Include all site staff working on a study, such as:
   - Clinicians
   - Physicians
   - Pharmacists
   - Data personnel
   - Any other individuals authorized to make entries and/or corrections on CRFs.
3. Key/log must include:
   - Initials
   - Printed Signature
   - Legal Signature, including first and last name
   - Credentials [if appropriate]
4. To document Principal Investigator delegation of study related task to staff.

### Unblinding

A copy of the Sponsor’s SOP for unblinding must be on file at the site.

### Source Document Template

To include original source document template and current version if applicable provided by sponsor related to trial.

### Audit Information

Form 483 [if applicable] and response [if applicable]

Any and all correspondence with FDA regarding the audit

### Record Retention

According to 21 CFR 312.62(c) and 21 CFR 812.140(b), an investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
References

- UC Davis IRB (http://research.ucdavis.edu/u/a/irb)
- Bioresearch Monitoring Unit of FDA (http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm)
Chapter 6: Appendices

Appendix 1

Summary of Good Clinical Practice (GCP) Principles

**FDA Guidance for Industry** (E6 Good Clinical Practice: Consolidated Guideline.60)

**Principle 1:** Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki; and that are consistent with GCP and the applicable regulatory requirements.

**Principle 2:** Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

**Principle 3:** The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

**Principle 4:** The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

**Principle 5:** Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

**Principle 6:** A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.

**Principle 7:** The medical care given to and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate of a qualified dentist.

**Principle 8:** Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

**Principle 9:** Freely given informed consent should be obtained from every subject prior to clinical trial participation.

**Principle 10:** All clinical trial information should be recorded handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

**Principle 11:** The confidentiality of records that could identify subjects should be projected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

**Principle 12:** Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

**Principle 13:** Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Appendix 2

Elements of Informed Consent Explained

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject’s participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

The statement that the study involves research is important because the relationship between patient-physician is different than that between subject-investigator. Any procedures relating solely to research (e.g., randomization, placebo control, additional tests) should be explained to the subjects. The procedures subjects will encounter should be outlined in the consent document, or an explanation of the procedures, such as a treatment chart, may be attached to and referenced in the consent document.

Consent documents for studies of investigational articles should include a statement that a purpose of the study includes an evaluation of the safety of the test article. Statements that test articles are safe or statements that the safety has been established in other studies, are not appropriate when the purpose of the study includes determination of safety. In studies that also evaluate the effectiveness of the test article, consent documents should include that purpose, but should not contain claims of effectiveness.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

The risks of procedures relating solely to research should be explained in the consent document. The risks of the tests required in the study protocol should be explained, especially for tests that carry significant risk of morbidity/mortality themselves. The explanation of risks should be reasonable and should not minimize reported adverse effects.

The explanation of risks of the test article should be based upon information presented in documents such as the protocol and/or investigator’s brochure, package labeling, and previous research study reports. For IND studies, the IRB should assure that the clinical investigator submits the investigator’s brochure (when one exists) with the other study materials for review.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

The description of benefits to the subject should be clear and not overstated. If no direct benefit is anticipated, that should be stated. The IRB should be aware that this element includes a description not only of the benefits to the subject, but to “others” as well. This may be an issue when benefits accruing to the investigator, the sponsor, or others are different than that normally expected to result from conducting research. Thus, if these benefits may be materially relevant to the subject’s decision to participate, they should be disclosed in the informed consent document.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

To enable a rational choice about participating in the research study, subjects should be aware of the full range of options available to them. Consent documents should briefly explain any pertinent alternatives to entering the study including, when appropriate, the alternative of supportive care with no additional disease-directed therapy. While this should be more than just a list of alternatives, a full risk/benefit explanation of alternatives may not be appropriate to include in the written document. The person(s) obtaining the subjects’ consent, however, should be able to discuss available alternatives and answer questions that the subject may raise about them. As with other required elements, the consent document should contain sufficient information to ensure an informed decision.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

Study subjects should be informed of the extent to which the institution intends to maintain confidentiality of records identifying the subjects. In addition, they should be informed that FDA may inspect study records (which include individual medical records). If any other entity, such as the sponsor of the study, may gain access to the study records, the subjects should be so informed. The consent document may, at the option of the IRB, state that subjects’ names are not routinely required to be divulged to FDA. When FDA requires subject names, FDA will treat such information as confidential, but on rare occasions, disclosure to third parties may be required. Therefore, absolute protection of confidentiality by FDA should not be promised or implied. Also, consent documents should not state or imply that FDA needs clearance or permission from the subject for access. When clinical investigators conduct a study for submission to FDA, they agree to allow FDA access to the study records. Informed consent documents should make it clear that, by participating in research, the subject’s records automatically become part of the research database. Subjects do not have the option to keep their records from being audited/reviewed by FDA.

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

Informed consent documents should describe any compensation or medical treatments that will be provided if injury occurs. If specific statements cannot be made (e.g., each case is likely to require a different response), the subjects should be informed where further information may be obtained. The consent should also indicate whether subjects will be billed for the cost of such medical treatments. When costs will be billed, statements such as “will be billed to you or your insurer in the ordinary manner,” “the sponsor has set some funds aside for medical costs related to...” are preferred. Statements such as: “will be the responsibility of you or your insurance company” or “compensation is not available,” could appear to relieve the sponsor or investigator of liability for negligence, see 21 CFR 50.20.

Compensation v. Waiver of Subject’s Rights

The consent document must explain whether there is compensation available in case of injury but must not waive or appear to waive the rights of the subject or release or appear to release
those conducting the study from liability for negligence. When no system has been set up to provide funds, the preferred wording is: “no funds have been set aside for” “[the cost] will be billed to you or your insurance,” or similar wording that explains the provisions or the process. Wording such as: “will be your responsibility or that of your third-party payor” has been erroneously interpreted by some subjects to mean the insurance company is required to pay.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects’ rights, and whom to contact in the event of a research-related injury to the subject.

This requirement contains three components, each of which should be specifically addressed. The consent document should provide the name of a specific office or person and the telephone number to contact for answers to questions about: 1) the research subjects’ rights; 2) a research-related injury; and 3) the research study itself. It is as important for the subject to know why an individual should be contacted as it is for the subject to know whom to contact. Although a single contact might be able to fulfill this requirement, IRBs should consider requiring that the person(s) named for questions about research subjects’ rights not be part of the research team as this may tend to inhibit subjects from reporting concerns and discovering possible problems.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

This element requires that subjects be informed that they may decline to participate or to discontinue participation at any time without penalty or loss of benefits. Language limiting the subject’s right to withdraw from the study should not be permitted in consent documents. If the subjects who withdraw will be asked to permit follow-up of their condition by the researchers, the process and option should be outlined in the consent document.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the 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.

A statement that there may be unforeseen risks to the embryo or fetus may not be sufficient if animal data are not available to help predict the risk to a human fetus. Informed consent documents should explain that mutagenicity (the capability to induce genetic mutations) and teratogenicity (the capability to induce fetal malformations) studies have not yet been conducted/completed in animals. [Note: The lack of animal data does not constitute a valid reason for restricting entry of women of childbearing potential into a clinical trial.] Subjects, both women and men, need to understand the danger of taking a drug whose effects on the fetus are unknown. If relevant animal data are available, however, the significance should be explained to potential subjects. Investigators should ensure that the potential risks that the study poses are adequately explained to subjects who are asked to enter a study. If measures to prevent pregnancy should be taken while in the study, that should be explained.
FDA guidance on the inclusion of women in clinical trials [58 FR 39406] now gives IRBs broader discretion to encourage the entry of a wide range of individuals into the early phases of clinical trials. FDA urges IRBs to question any study that appears to limit enrollment based on gender and/or minority status. Statements such as, “you may not participate in this research study if you are a woman who could become pregnant” should not routinely be included in informed consent documents.

(2) Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent.

When applicable, subjects should be informed of circumstances under which their participation may be terminated by the investigator without the subject’s consent. An unexplained statement that the investigator and/or sponsor may withdraw subjects at any time, does not adequately inform the subjects of anticipated circumstances for such withdrawal. A statement that the investigator may withdraw subjects if they do not “follow study procedures” is not appropriate. Subjects are not in a position to know all the study procedures. Subjects may be informed, however, that they may be withdrawn if they do not follow the instructions given to them by the investigator.

(3) Any additional costs to the subject that may result from participation in the research.

If the subjects may incur an additional expense because they are participating in the research, the costs should be explained. IRBs should consider that some insurance and/or other reimbursement mechanisms may not fund care that is delivered in a research context.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

When withdrawal from a research study may have deleterious effects on the subject’s health or welfare, the informed consent should explain any withdrawal procedures that are necessary for the subject’s safety and specifically state why they are important to the subject’s welfare. An unexplained statement that the subject will be asked to submit to tests prior to withdrawal, does not adequately inform the subjects why the tests are necessary for the subject’s welfare.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.

When it is anticipated that significant new findings that would be pertinent to the subject’s continued participation are likely to occur during the subject’s participation in the study, the IRB should determine that a system, or a reasonable plan, exists to make such notification to subjects.

(6) The approximate number of subjects involved in the study.

If the IRB determines that the numbers of subjects in a study is material to the subjects’ decision to participate, the informed consent document should state the approximate number of subjects involved in the study.
Appendix 3.

EXPERIMENTAL SUBJECT’S BILL OF RIGHTS

Medical Research Studies

The rights below are the rights of every person who is asked to be in a medical research study. As an experimental subject, you have the following rights:

1) To be told what the study is trying to determine.
2) To be told what will happen to you and whether any of the procedures, drugs, or devices is different from what would be used in standard practice.
3) To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen to you for research purposes.
4) To be told if you can expect any benefit from participating and, if so, what the benefit might be.
5) To be told the other choices you have and how they may be better or worse than being in the study.
6) To be allowed to ask any questions concerning the study, both before agreeing to be involved and during the course of the study.
7) To be told what sort of medical treatment is available if any complications arise.
8) To refuse to participate or to change your mind about participating after the study is started. This decision will not affect your right to receive the care you would receive if you were not in the study.
9) To receive a copy of the signed and dated consent form.
10) To be free of pressure when considering whether you wish to agree to be in the study.

If you have other questions, please ask the researcher or research assistant. In addition, you may contact the Institutional Review Board, which is concerned with protecting volunteers in research projects. You may reach the IRB office by calling (916) 703-9151, from 8:00 a.m. to 5:00 p.m., Monday through Friday, or by writing to the Institutional Review Board, Clinical and Translational Science Center, Suite 1400, Rm. 1429, 2921 Stockton Blvd., Sacramento, California 95817.

_____________________________       __________________________
Signature of Subject or    Date
Legal Representative
Appendix 4

HIPAA Form

University of California
Permission to Use Personal Health Information for Research

Study Title (or IRB Approval Number if study title may breach subject’s privacy):

Sponsor/Funding Agency (if funded):

A. What is the purpose of this form?
State and federal privacy laws protect the use and release of your health information. Under these laws, the University of California or your health care provider cannot release your health information to the research team unless you give your permission. The research team includes the researchers and people hired by the University or the sponsor to do the research. If you decide to give your permission and to participate in the study, you must sign this form as well as the Consent Form. This form describes the different ways that the researcher, research team and research sponsor may use your health information for the research study. The research team will use and protect your information as described in the attached Consent Form. However, once your health information is released it may not be protected by the privacy laws and might be shared with others. If you have questions, ask a member of the research team.

B. What Personal Health Information will be released?
If you give your permission and sign this form, you are allowing your health care provider to release the following medical records containing your Personal Health Information. Your Personal Health Information includes health information in your medical records and information that can identify you. For example, Personal Health Information may include your name, address, phone number or social security number.

- Entire Medical Record
- Radiology Reports
- Pathology Reports
- Laboratory Reports
- Dental Records
- Operative Reports
- Emergency Medicine Center Reports
- Other: ______________________________________________________________________
- Progress Notes
- History & Physical Exams
- Discharge Summary
- Consultations
- EKG
- Radiology images
- Psychological Tests
- Health Care Billing Statements
- Outpatient Clinic Records

C. Do I have to give my permission for certain specific uses?

Yes. The following information will only be released if you give your specific permission by putting your initials on the line(s).

____ I agree to the release of information pertaining to drug and alcohol abuse, diagnosis or treatment.

____ I agree to the release of HIV/AIDS testing information.

____ I agree to the release of genetic testing information.

____ I agree to the release of information pertaining to mental health diagnosis or treatment as follows: ______________________________________________.

D. How will my Personal Health Information be used?

Your Personal Health Information may be released to these people for the following purposes:

1. To the research team for the research described in the attached Consent Form;
2. To others at UC who are required by law to review the research;
3. To others who are required by law to review the quality and safety of the research, including: U.S. government agencies, such as the Food and Drug Administration, the research sponsor or the sponsor’s representatives, or government agencies in other countries. These organizations and their representatives may see your Personal Health Information. They may not copy or take it from your medical records unless permitted or required by law.

E. How will my Personal Health Information be used in a research report?

If you agree to be in this study, the research team may fill out a research report. (This is sometimes called “a case report”.) The research report will not include your name, address, or telephone or social security number. The research report may include your date of birth, initials, dates you received medical care, and a tracking code. The research report will also include information the research team collects for the study. The research team and the research sponsor may use the research report and share it with others in the following ways:

1. To perform more research;
2. Share it with researchers in the U.S. or other countries;
3. Place it into research databases;
4. Use it to improve the design of future studies;
5. Use it to publish articles or for presentations to other researchers;
6. Share it with business partners of the sponsor; or
7. File applications with U.S. or foreign government agencies to get approval for new drugs or health care products.
F. Does my permission expire?

This permission to release your Personal Health Information expires when the research ends and all required study monitoring is over. Research reports can be used forever.

G. Can I cancel my permission?

You can cancel your permission at any time. You can do this in two ways. You can write to the researcher or you can ask someone on the research team to give you a form to fill out to cancel your permission. If you cancel your permission, you may no longer be in the research study. You may want to ask someone on the research team if canceling will affect your medical treatment. If you cancel, information that was already collected and disclosed about you may continue to be used. Also, if the law requires it, the sponsor and government agencies may continue to look at your medical records to review the quality or safety of the study.

H. Signature

If you agree to the use and release of your Personal Health Information, please sign below. You will be given a signed copy of this form.

Subject’s Name (print)

Subject’s Signature Date

Note: if the subject is a minor, an individual signing with an “X”, an adult incapable of giving consent, or is unable to read the authorization, fill out and attach the “special signatures” page (sections “I” and “J”).

SPECIAL SIGNATURES PAGE

I. If the subject is a minor, or an individual signing with an “X”, or an adult incapable of giving consent (where IRB approved), the legally authorized representative or witness signs here:

Legally Authorized Representative’s Name Relationship to the Subject or Witness to the “X” (print)

Representative or Witness Signature Date
J. If the subject is unable to read the authorization, the translator or reader and a witness sign here:

I have accurately and completely read this Authorization to ____________________ (subject’s name) in ________________(language), the subject’s primary language. The subject has verbally affirmed his/her Authorization to me and to the witness.

___________________________________________________________________________
Translator or Reader’s Name (print)

___________________________________________________________________________
Translator or Reader’s Signature   Date

___________________________________________________________________________
Witness Name (print)

___________________________________________________________________________
Witness Signature     Date
Appendix 5. Sample Case Report Form

<table>
<thead>
<tr>
<th>NAME OF THE STUDY</th>
<th>SCREENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site Number</td>
<td>Subject Number</td>
</tr>
<tr>
<td></td>
<td>d d / m m m / y y y y</td>
</tr>
</tbody>
</table>

**INFORMED CONSENT**
- Date of Signed Informed Consent: dd / mm m / yyyy
- Date of Assent / Waiver of Assent: dd / mm m / yyyy
- If Not Applicable (N/A), Reason: ________________

**DEMOGRAPHICS**
- Date of Birth: dd / mm m / yyyy
- Gender (check one box): Male, Female
- Ethnicity (check one box): Not Hispanic or Latino, Hispanic or Latino
- Race (check all that apply): American Indian or Alaska Native, Asian, Black or African American, White, Native Hawaiian or Other Pacific Islander, Other (specify): ________________

**SCREENING TESTS**
- Date SCQ Completed: dd / mm m / yyyy
- Date DSM-IV-TR Completed: dd / mm m / yyyy
- Date ADI-R Completed: dd / mm m / yyyy
- Reason Codes: 1 = Child Refused, 2 = Parent Refused, 3 = Child Uncooperative, 4 = Child Ill, 5 = Other (specify): ________________

**STOOL SAMPLE**
- Date Stool Sample Collected: dd / mm m / yyyy
- Account Number: mm m m m m
- Requisition Number: mm m m m m
- Not Done: If Not Done, Reason: ________________
### Appendix 6. Comparison of Abbreviated and Full IDE Requirements  
(Adapted from CRA Handbook, 2009)

The investigational device exemptions allow for two levels of approval for clinical investigations. The lower level of approval – for non-significant risk devices – requires IRB approval but not FDA approval and compliance with the abbreviated requirements of the IDEs. The higher level of approval – for significant risk devices – requires both IRB and FDA approval for the investigation and compliance with the full requirements of the IDEs. The abbreviated and full requirements are compared in the table.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Item</th>
<th>Abbreviated</th>
<th>Full</th>
</tr>
</thead>
<tbody>
<tr>
<td>812.5</td>
<td>Labeling requirements</td>
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<tr>
<td>812.5(a)</td>
<td>“Caution: Investigational Device” statement</td>
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<tr>
<td>812.5(a)</td>
<td>Contradictions, hazards, adverse effects, interfering substances or devices, warnings and precautions</td>
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<tr>
<td>812.7</td>
<td>Prohibition of promotion</td>
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<td>812.20</td>
<td>IDE Application submitted to FDA</td>
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<tr>
<td>812.20(b)(2)</td>
<td>Report of Prior Investigations</td>
<td>x</td>
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<tr>
<td>812.20(b)(2)</td>
<td>Summary of Investigational Plan</td>
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<tr>
<td>812.20(b)(3)</td>
<td>Description of manufacturing</td>
<td>x</td>
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<tr>
<td>812.20(b)(4)</td>
<td>Example Investigator Agreements, names &amp; address of investigators</td>
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<td>812.20(b)(5)</td>
<td>Certification that investigators will follow agreement</td>
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<td>812.20(b)(6)</td>
<td>Name, address and chairperson of each reviewing IRB</td>
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<td>812.20(b)(7)</td>
<td>Name and address of investigational institutions</td>
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<tr>
<td>812.20(b)(8)</td>
<td>Cost, if device is sold, and why sale does not constitute commercialization of device</td>
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<td>812.20(b)(9)</td>
<td>Environmental assessment of exclusion</td>
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**Investigational Plan**

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<td>Protocol</td>
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<td>812.25(c)</td>
<td>Risk Analysis</td>
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<td>812.25(d)</td>
<td>Description of device</td>
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<td>812.25(e)</td>
<td>Monitoring procedures</td>
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<td>812.25(f)</td>
<td>Labeling</td>
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<td>812.25(g)</td>
<td>Consent materials</td>
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<td>812.25(h)</td>
<td>IRB information</td>
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<td>812.25(i)</td>
<td>Other institutions</td>
<td>x</td>
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<tr>
<td>812.25(j)</td>
<td>Additional records &amp; reports</td>
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</table>

**Report of Prior Investigations**

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<td>Adverse information, published and unpublished</td>
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<td>Copies of significant publications</td>
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<td>Summary of unpublished information</td>
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<td>812.27(b)(3)</td>
<td>Nonclinical laboratory studies and statement of GLP compliance</td>
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<td>Citation</td>
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<td>812.40</td>
<td>Responsibilities of Sponsors</td>
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<td>812.40</td>
<td>Select qualified investigators</td>
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<tr>
<td>812.40</td>
<td>Provide investigators with needed information to conduct study</td>
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<tr>
<td>812.40</td>
<td>Ensure IRB approval obtained</td>
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<tr>
<td>812.40</td>
<td>Inform FDA and IRB of new information</td>
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<td>812.42</td>
<td>Ensure IDE approval by FDA obtained</td>
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<td>812.42</td>
<td>Await IRB and FDA approval</td>
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<td>812.43</td>
<td>Selecting Investigators and Monitors</td>
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<td>812.43(a)</td>
<td>Select qualified investigators</td>
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<td>812.43(b)</td>
<td>Ship device only to investigators</td>
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<td>812.43(c)</td>
<td>Obtain investigator agreement</td>
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<td>Obtain investigator financial information</td>
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<td>(Financial Disclosure guideline, Q12)</td>
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<td>Select monitors</td>
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<td>Monitoring Investigations</td>
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<td>812.46(a)</td>
<td>Secure investigator compliance</td>
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<td>812.46(b)</td>
<td>Terminate study if unanticipated adverse effects present unreasonable risk</td>
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<td>812.46(c)</td>
<td>Resume with IRB or IRB/FDA approval</td>
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<td>812.60</td>
<td>IRB compliance with Part 56 [See 812.2(b)(ii)]</td>
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<td>IRB review and approval</td>
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<td>812.64</td>
<td>IRB continuing review</td>
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<td>812.66</td>
<td>Notify investigator and FDA if IRB finds device to be significant risk</td>
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<tr>
<td>812.100</td>
<td>Responsibilities of Investigators</td>
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<tr>
<td>812.100</td>
<td>Follow signed agreement, investigational plan, and FDA regulations</td>
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<tr>
<td>812.110(a)</td>
<td>Obtain informed consent [See 812.2(b)(iii)]</td>
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<td>812.110(b)</td>
<td>Await IRB and FDA approval</td>
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<td>812.110(c)</td>
<td>Comply with signed agreement, investigational plan and FDA regulations</td>
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<td>812.110(d)</td>
<td>Supervise device use</td>
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<td>812.110(e)</td>
<td>Disclose financial information</td>
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<td>812.110(f)</td>
<td>Return or dispose of remaining devices</td>
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<td>Receipt, use or disposition of device</td>
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<td>812.140(a)(3)</td>
<td>Case history &amp; device exposure</td>
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<td>Signed and dated informed consent</td>
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<td>812.140(a)(3)(ii)</td>
<td>Relevant observations</td>
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<td>812.140(a)(3)(iii)</td>
<td>Record of device exposure</td>
<td>x</td>
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<td>812.140(a)(4)</td>
<td>Protocol and deviations</td>
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<td>Other FDA required records</td>
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<td>Abbreviated</td>
<td>Full</td>
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<td>812.140(b)</td>
<td><strong>Sponsor Records</strong></td>
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<td>Shipment &amp; disposition of device</td>
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<td>Investigator Agreement</td>
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<td>Financial disclosure</td>
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<td>812.140(b)(4)(i)</td>
<td>Name and use of device</td>
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<td>812.140(b)(4)(ii)</td>
<td>Explanation of why not significant risk</td>
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<td>812.140(b)(4)(iii)</td>
<td>Name &amp; address of each investigator</td>
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<td>812.140(b)(4)(iv)</td>
<td>Name &amp; address of IRBs</td>
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<td>812.140(b)(4)(v)</td>
<td>Statement regarding GMP compliance</td>
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<td>812.140(d)</td>
<td>Two-year record retention</td>
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| 812.150(a)   | **Investigator Reports**                         |             |                    |
| 812.150(a)(1)| Unanticipated adverse effects                    | x           |                    |
| 812.150(a)(2)| Withdrawal of IRB approval                       | x           |                    |
| 812.150(a)(3)| Progress reports                                  | x           |                    |
| 812.150(a)(4)| Deviations from protocol                        | x           |                    |
| 812.150(a)(5)| Informed consent omission                        | x           |                    |
| 812.150(a)(6)| Final report                                     | x           |                    |
| 812.150(a)(7)| Other                                           | x           |                    |

| 812.150(b)   | **Sponsor Reports**                              |             |                    |
| 812.150(b)(1)| Unanticipated adverse effects                    | x           |                    |
| 812.150(b)(2)| Withdrawal of IRB approval                       | x           |                    |
| 812.150(b)(3)| Withdrawal of FDA approval                       | x           |                    |
| 812.150(b)(4)| Current investigator list                        | x           |                    |
| 812.150(b)(5)| Progress reports                                  | x           |                    |
| 812.150(b)(6)| Recall and device disposition                    | x           |                    |
| 812.150(b)(7)| Final report                                     | x           |                    |
| 812.150(b)(8)| Omission of informed consent report              | x           |                    |
| 812.150(b)(9)| Significant risk determination report            | x           |                    |
| 812.150(b)(10)| Other FDA or IRB required reports               | x           |                    |
Appendix 7. Helpful links

AMA-American Medical Association: http://www.ama-assn.org/

ACRP-Association of Clinical Research Professionals: http://www.acrpn.org/

BIMO-Bioresearch and Monitoring: http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm

CDER-Center for Drug Evaluation and Research: http://www.fda.gov/Drugs/default.htm

CDRH-Center for Devices and Radiological Health: http://www.fda.gov/MedicalDevices/default.htm

Center Watch: http://www.centerwatch.com/

ClinicalTrials gov: http://clinicaltrials.gov/


DIA-Drug Information Association: http://www.diahome.org/

FDA-Food and Drug Administration: http://www.fda.gov/


Glossary of Clinical Trial Terms: http://www.clinicaltrials.gov/ct2/info/glossary

HHS-US Department of Health and Human Services: http://www.hhs.gov/

HIPAA-Health Insurance Portability and Accountability Act: http://www.hhs.gov/ocr/privacy/


MAGI-Model Agreements and Guidelines International: http://magiworld.org/

NIH-National Institutes of Health: http://www.nih.gov/

OHRP-Office for Human Research Protection: http://www.hhs.gov/ohrp/

RAPS-Regulatory Affairs Professional Society: http://www.raps.org/


UC Davis CTSC-Clinical and Translational Science Center: http://www.ucdmc.ucdavis.edu/ctsc/
Appendix 8. Index

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21 CFR 11: 93
21 CFR 50: 13, 16, 18, 22, 111
21 CFR 54: 100
21 CFR 56: 10, 56
21 CFR 58: 104
21 CFR 58: 104
21 CFR 58: 104
21 CFR 312: 4, 16, 27, 28, 45, 68, 89, 92, 107
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