Introduction

The purpose of this Guidebook is to provide 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. 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 investigators and their staff navigate through the various requirements of clinical research at UC Davis. The Guidebook is not meant to be all inclusive; more help is available 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), Health System Compliance (http://www.ucdmc.ucdavis.edu/compliance/) and Health System Contracts – Clinical Trials Contracts (http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/).

This Guidebook references materials from other sources with references cited whenever possible. Every effort was made to ensure the information is accurate as of the date of the publication. Although the information found in this Guidebook is believed to be reliable, no warranty, expressed or implied, is made regarding the accuracy, adequacy, completeness, legality, reliability, or usefulness of any information, either isolated or in the aggregate. The information is provided “as is.” The authors are not responsible for the content of any referenced or linked page and are not liable for that content. The documents and related graphics could contain technical inaccuracies or typographical errors. The authors are not liable for any improper or incorrect use of the information contained in this Guidebook and assume no responsibility for anyone’s use of the information.

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ACTIVITY #1: Complete Necessary 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 protecting research participants.

1.1 Become Aware of Laws Governing Clinical Research

1.1.1 Department of Health and Human Services (HHS)

HHS is the government’s principal 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).

Food and Drug Administration (FDA) is responsible for protecting and promoting public health through the regulations 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 (www.fda.gov). Understanding these rules is critical for any investigator who conducts human subject studies with drugs, devices or dietary supplements, whether already approved on the market or still investigational.

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 HHS. OHRP performs these services through providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and

**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 (www.nih.gov). As of April 2013, the NIH funds 61 Clinical and Translational Science Centers around the country.

Working together as a national consortium, Clinical Translational Science Award (CTSA) institutions share a common vision to improve human health by transforming the research and training environment to enhance the efficiency and quality of clinical and translational research. The CTSA program is supported by the National Center for Advancing Translational Science (NCATS), part of the National Institutes of Health. The CTSA program has the following overriding objectives:

1. Provide a comprehensive array of essential tools and services to spark clinical and translational research.
2. Ensure the training of a well prepared workforce of trainees, staff, and investigators.
3. Effectively communicate the many tools, services, and training opportunities to ensure innovative translational science advances that will improve human health.

Today, the **UC Davis CTSC** (www.ucdmc.ucdavis.edu/ctsc) offers a robust toolbox of resources that faculty, trainees, and staff across the scientific and medical spectrum can use to enhance research and improve health and health-care delivery. The Clinical Trials Resource Group, author of this guidebook, is a program at the UC Davis CTSC.

**Centers for Medicare and Medicaid Services (CMS)** is the US Federal agency which administers Medicare, Medicaid, and the Children’s Health Insurance Program (www.cms.gov). 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 participating in clinical trials.” CMS responded to the executive order with the clinical trial policy - National Coverage Determination (NCD). Medicare State fiscal intermediaries also issue Local Coverage Determinations (LCD). As of August 2013, California’s intermediary is Noridian. Understanding coverage rules is critical for generating correct billing claims for clinical research participants. Starting in 2013 the Affordable Care Act will strengthen the provision for insurance coverage for individuals participating in
clinical trials. Insurers will be prohibited from dropping or limiting coverage because an individual chooses to participate in a clinical trial. This applies to all clinical trials that treat cancer or other life-threatening diseases.

At UC Davis, the tool and the process of applying CMS rules to each individual study is called Coverage Analysis. This information is reviewed in detail in Activity#4 of this Guidebook.

1.1.2 Code of Federal Regulations

The Code of Federal Regulations (CFR; https://ecfr.gpoaccess.gov) is a compendium of 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 regulations. 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) is a core set of regulations defining protection of Human Subjects in clinical research. 45 CFR part 46 includes four subparts: subpart A, also known as the Federal Policy or the “Common Rule”; subpart B, additional protections for pregnant women, human fetuses, and neonates; subpart C, additional protections for prisoners; and subpart D, additional protections for children. Through a system of IRB registration and assurances, HHS regulations require institutions to commit to compliance with 45 CFR 46 before initiating participation in HHS-conducted or -supported research involving human subjects.

The main elements of the Common Rule include:

What human research issues are addressed in 45 CFR part 46? (from answers.hhs.gov)

HHS regulations at 45 CFR part 46 stipulate substantive and procedural requirements for investigators and institutions engaged in HHS-supported or -conducted research. Specifically, in addition to providing definitions and information about application of the regulations, specific sections of the regulations address the following topics:

- Assuring compliance with the regulations (46.103)
- Institutional Review Board (IRB) membership (46.107)
- IRB functions and operations (46.108)
- IRB review of research (46.109)
- Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research (46.110)
• Criteria for IRB approval of research, including minimizing risk, ensuring confidentiality, and protecting vulnerable populations, (46.111)
• Review by institution (46.112)
• Suspension or termination of IRB approval of research (46.113)
• Cooperative research (46.114)
• IRB records (46.115)
• General requirements for informed consent (46.116)
• Documentation of informed consent (46.117)
• Applications and proposals lacking definite plans for involvement of human subjects (46.118)
• Research undertaken without the intention of involving human subjects (46.119)
• Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency (46.120)
• Use of Federal funds (46.122)
• Early termination of research support: Evaluation of applications and proposals (46.123)
• Conditions (46.124)

Additional protections for specific populations have been adopted by HHS (and other departments and agencies to a lesser extent), as follows:

- **Subpart B**, Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- **Subpart C**, Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- **Subpart D**, Additional Protections for Children Involved as Subjects in Research

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 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. UC Davis’ Federalwide Assurance Number (FWA#) is 00004557, and is approved up to June 28, 2016

Since 1991, 45 CFR Part 46 was formally adopted by more than a dozen other Departments and Agencies that conduct or fund research involving human subjects.” The Department of Veterans Affairs promulgated this same rule at 38 CFR Part 16. Today, this Federal Policy is shared by 17 Departments and Agencies, representing most, but not all, of the federal Departments and Agencies sponsoring human-subjects research.
Title 21 CFR
The FDA regulations (Title 21 CFR) 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 according to 21 CFR Parts 50 and 56. Title 21 CFR part 50 defines regulations for informed consent and 21 CFR part 56 defines regulations for IRBs. These regulations largely overlap but are not identical with the Common Rule. Investigators need to know both sets of regulations to apply them appropriately.

Title 21 CFR 312 details the regulations for human research with investigational drugs. This section includes, but is not limited to, the regulations for applying to FDA to conduct research under an Investigational New Drug (IND) application (21 CFR 312 Subpart B), responsibilities of Sponsors and Investigators under an IND (21 CFR 312 Subpart D), and expanded access to Investigational Drugs (21 CFR 312 Subpart I). Activity #3 of this Guidebook discusses the drug development process in more detail.

Title 21 CFR 812 details the regulations for human research with investigational devices. The regulations lay out the framework for applying to FDA to conduct human subjects research with Investigational Devices (21 CFR 812 Subpart B), responsibilities of Sponsors (21 CFR 812 Subpart C) and Investigators (21 CFR 812 Subpart E), and IRB approval (21 CFR 812 Subpart D). Activity #3 of this Guidebook discusses the device development process in more detail.

1.2 UC Davis Clinical Research Guidebook (current edition)
The UC Davis Clinical Research Guidebook is updated on an annual basis to provide updates and new information. Always reference the most recent edition.

1.3 Clinical Trials SOPs housed by CTSC
The CTSC creates and maintains multiple SOPs related to conduct of clinical research at UC Davis. These SOPs can be found on the Clinical Trials website. For convenience, the same website houses links to IRB SOPs and UCDHS policies and procedures: http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml

As of date of publication, the CTSC promulgated the following SOPs:

SOP#1 Training and Development Requirements (updated 02/08/2012)
SOP#2 Roles and Responsibilities of the Research Team (updated 02/08/2012)
SOP#3 CTSC Mentoring Program for CRCs (updated 03/14/2013)
SOP#4 Coverage Analysis (updated 04/15/2013)
SOP#5 Budget Approval for Industry Initiated Studies (updated 03/14/2013)
SOP#6 Development of Clinical Trial Budgets for Grant Proposals (updated 04/15/2013)
1.4 **Human Subjects Research (CITI) Training**

UC Davis employs the Collaborative Institutional Training Initiative (CITI) program—a web based training program to satisfy the training requirements for all personnel conducting human subject research at UC Davis. CITI offers two versions of the Basic Human Research Training course: one for Biomedical Investigators and one for Social & Behavioral Investigators. A module on good clinical practice (GCP) is also required for individuals conducting clinical trials. Certification is valid for 3 years. For more information, please see [http://research.ucdavis.edu/c/cs/hrp/res/roe](http://research.ucdavis.edu/c/cs/hrp/res/roe)

1.5 **UCDHS Mandatory Annual Training**

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. For more information, please see [http://www.ucdmc.ucdavis.edu/cppn/mat](http://www.ucdmc.ucdavis.edu/cppn/mat)

1.6 **UCDHS Privacy and Security Training**

The objectives of the training are to understand what information must be protected under State and Federal privacy laws and what rights patients have regarding access and use of their medical information. It also addresses the role of the employee in maintaining privacy and security of medical data and the consequences of non-compliance. For more information, please see [http://www.ucdmc.ucdavis.edu/compliance/Quiz/PrivacySecurity/player.html](http://www.ucdmc.ucdavis.edu/compliance/Quiz/PrivacySecurity/player.html)

1.7 **Dangerous Goods Shipping for Infectious Substances and Dry Ice Training**

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](http://lms.ucdavis.edu)
1.8 Lab Safety Training or Biological Safety, Chemical/Laboratory Safety, and Hazardous Waste Management and Minimization

The Lab Safety training is geared toward School of Medicine employees. The campus offers the Biological Safety, Chemical/Laboratory and Safety, and Hazardous Waste Management and Minimization, which is an in-depth course, covering all biological hazards. The Biological Safety and Hazardous Waste courses are required for anyone working in research and related projects that involve:

a. Infectious agents (human, animal, or plant)
b. Recombinant DNA unless exempted under the NIH Guidelines for Research Involving Recombinant DNA Molecules
c. Human and non-human primate, tissues, body fluids, or cultured cells (including cell lines)
d. Potential exposure to blood borne pathogens
e. Medical waste management

Register at: http://safetyservices.ucdavis.edu/tr

1.9 IRB New Submitter Training

New Submitter Training is conducted by the IRB. This orientation provides detailed training on the ethical principles of human research, an explanation of the researcher’s primary responsibility for protecting research subjects and for complying with all applicable provisions of institutional, state and federal laws. It provides an explanation of the different levels of IRB review and describes the processes for IRB submissions.

For more information, please see http://research.ucdavis.edu/c/cs/hrp/out.

In addition, an Investigator Manual is available as a guide for the policies and procedures related to the conduct of Human Research that are specific to UC Davis. The document discusses the mechanics of working with the IRB and Human Research Protection Program.

For more information, please see http://research.ucdavis.edu/c/cs/hrp/documents/HRP103INVESTIGATORMANUAL.docx

1.10 CTSC Clinical Trials Education and Training Program

The UC Davis Clinical Trials Resource Group, a CTSC program, makes education and training outreach a high priority. The curriculum delivers practical knowledge for GCP implementation on site. Information delivery is structured in three tiers: 1) general information about what is new in the clinical research arena, 2) information pertinent to UC Davis-specific knowledge areas and in-depth training on UC Davis processes, and 3) procedures. The program delivers information via the following formats: web-based seminars and monthly updates, in-service and small
group training, one-on-one mentoring program, a blog, a newsletter, a guidebook, several process maps and checklists, and a comprehensive website.

Monthly newsletters contain short informational articles with policy changes, process clarifications and announcements. The same information is presented during the monthly teleconferences, accompanied by power point presentations and live demonstrations. Clinical Research Process Maps, a visual step-by-step guide, are designed to assist with navigation of clinical trials administrative processes in an easy to follow, at-a-glance format. Separate Process Maps are created for Interventional Trials, Non-Interventional Studies (i.e. chart reviews) and Social-Behavioral Studies. A Supplemental Checklist bridges the Guidebook and Process Maps and serves as a tool for those who wish to visually track their progress through the administrative landscape. These tools are required reading for new clinical research coordinators entering the CRC Mentoring program. More experienced investigators and staff can attend the monthly SoCRA Brown Bag seminars featuring content experts from around the country addressing new developments in clinical research, or Clinical Trials Workshops, focusing on UC Davis programs. CRC Basic courses work with small groups of coordinators to study in depth the best practices for GCP implementation on site.

For more information, please see http://www.ucdmc.ucdavis.edu/clinicaltrials/Forinvestigators/index.html

1.11 In Service Trainings: Coverage Analysis and Internal Budgets

In-Service training is available for both Coverage Analysis and internal budgets. For more information contact Suzan Bruce (916-703-0120) or Julie Calahan (916-734-2547).

Also see http://www.ucdmc.ucdavis.edu/clinicaltrials/BudgetingBilling/index.html

1.12 Financial Conflict of Interest Training

On August 24, 2012, new and more stringent rules for the disclosure of financial interests took effect for all research sponsored by the Public Health Service (PHS), including the National Institutes of Health (NIH). The new rules also apply to a handful of non-federal sponsors, including the American Cancer Society and the American Heart Association.

These new PHS financial conflict of interest (FCOI) rules apply to all “investigators” who engage in any research funded by a covered agency. “Investigators” are defined by PHS to include principal investigators and any other individual who, regardless of title or position, have responsibility for the design, conduct, or reporting of such covered research. This includes, for example, any graduate student or post-doctoral fellow who meets the definition of investigator.
All investigators who are engaged in any research funded by a covered entity as of August 24, 2012 must complete this training prior to the receipt of any new funds from the covered entity via a Notice of Award. All investigators who will engage in research funded by a covered entity after August 24, 2012 must complete the training prior to engaging in the research following receipt of funds via a Notice of Award. Any investigator who is added to an existing research project after August 24, 2012 must complete the training prior to engaging in any research on the project.

Each investigator must separately submit to the Institution (UC Davis’ Research Compliance and Integrity) a financial disclosure statement. The Disclosure must identify financial interests of the investigator, spouses/registered domestic partners, and dependent children that exceed the thresholds set by PHS and that relate to any of the investigator’s institutional responsibilities.

Disclosures must be made: (1) prior to the Notice of Award issue date for additional funds if you are already conducting covered research as of August 24, 2012; (2) no later than at the time of application for funding from a covered agency if the application is submitted after August 24, 2012; (3) annually; and (4) within 30 days after acquiring or discovering a financial interest that must be disclosed as defined by PHS.

Both COI Mandatory Training and Mandatory Disclosure form can be found on the Research Compliance and Integrity Website: http://research.ucdavis.edu/c/cs/ci
ACTIVITY #2: Study Development and Feasibility

2.1 Assistance with Study Start Up and Maintenance

The UC Davis Clinical and Translational Science Center (CTSC) can provide a wide range of consultation services during all stages of research, including development and start-up. All applicants interested in consultation services from CTSC are asked to fill out an Application for Resource Use (AFRU, http://www.ucdmc.ucdavis.edu/ctsc/). You will need your UC Davis Login ID and Kerberos passphrase to create the request.

Coverage Analysis for Investigator-initiated and Industry-initiated Studies

A Coverage Analysis is mandatory for all studies that include billing of patient care services in the UC Davis Health System. The Principal Investigator is ultimately responsible for ensuring that the Qualifying Clinical Trials (QCT) Form and Billing Grid are accurate. Both forms must be approved and signed by the principal investigator. The Department will store a paper or electronic copy on file (in the Study Financial Binder) for audit purposes. These documents are required at IRB submission. CTSC SOPs #4 and #6 provide further information http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml

Budget Estimates for Grant-sponsored or Department Sponsored Studies (CTSC SOP#6)

When the research team develops the description of the study (clinical trial protocol) and needs help with preparation of study budgets, the team is strongly encouraged to contact the CTSC Clinical Trial Resource Group (http://www.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/) for feasibility analysis of the protocol to ensure compliance with clinical research billing requirements, and to prepare correct budgets for patient care costs and other research activities. Briefly, the CTSC Clinical Trial Resource group will provide analysis of:

- The billing matrix of patient care services/procedures involved in the protocol (called Coverage Analysis).
- Hospital/clinic costs for study-related procedures and services that are not covered by insurance and therefore must be paid by study budgets.
- Operational Feasibility
- Regulatory Requirements (FDA and IRB)
- Other Clinical Trial Expenses

For detailed description see Activity #4.1.1 and CTSC SOP#6
Coordinator for Hire and New CRC Mentoring Program

It is a Department/Center responsibility to ensure that new staff members are qualified to participate in clinical research based on their education and training. If the Department/Center is unable to provide an adequate mentoring or training support, the CTCS CRC Mentoring Program can provide this service.

The CTSC CRC Mentoring Program is a one-on-one mentoring program for UCD Clinical Research Coordinators and other research staff in a CRC function role. Clinical Research Coordinators and research staff that function in a CRC role are able to participate at the discretion of their home Departments/ORUs. Preference is given to those participating in FDA-regulated clinical trials with drugs, devices or dietary supplements. The program is provided for a maximum of 10 hours of face-to-face training with a CTSC mentor. Department funding is required for the trainee to enter the program.

Mentoring Program Goals:
- Expand knowledge of resources for clinical trials education and training
- Provide individual personalized mentoring based on the mentee’s level of skills, knowledge and experience.

Mentee’s Goals:
- Assess current level of skills and knowledge
- Receive personalized education and training plan
- Receive hands-on training for selected areas of core expertise
- Increase comfort level in job responsibilities

For more details, see CTSC SOP#3

In addition, the Clinical Trials Group provides CRC-for-Hire on an hourly recharge basis.

Monitoring and Quality Assurance

The Clinical Trials Resource Group offers assistance with monitoring and quality assurance to all investigator-initiated studies. This program helps ensure compliance with FDA, GCP, and IRB regulations, and UC Davis Health System SOPs and P&Ps as related to clinical research. The activities offered aim to provide a proactive (rather than “for cause”) regulatory assessment and has a strong educational component.

For further information see http://www.ucdmc.ucdavis.edu/clinicaltrials/Monitoring/index.html
IRB Documents
The Clinical Trials Resource Group can help with IRB document preparation according to the latest IRB requirements. In particular, this service aims to assist with rapid start-up for industry-initiated trials.

For more information see http://www.ucdmc.ucdavis.edu/clinicaltrials/Forinvestigators/index.html

REDCap
REDCap (Research Electronic Data Capture) is a secure web application for building and managing online databases for research. Using REDCap’s streamlined process for rapidly developing projects, you may create and design projects by constructing a ‘data dictionary’ template file in Microsoft Excel, which can be later uploaded into REDCap. REDCap provides audit trails for tracking changes and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages. Also included are a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields.

For more information see http://www.ucdmc.ucdavis.edu/ctsc/redcap/

Biostatistics
The CTSC Biostatistics Group assists researchers with all sizes and types of projects, from simple data analyses to large, multi-center clinical trials. Specific services we can provide include grant proposal preparation, study design/sample size calculation, statistical analysis plan, data analysis and interpretation, statistical advice only, manuscript review and preparation, response to reviewer comments.

For more information see http://www.ucdmc.ucdavis.edu/ctsc/area/biostatistics/index.html

Identify Potential Cohort for Recruitment
A pool of potential study subjects can be estimated 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. 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 identified, 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.
CTSC Clinical Research Center (CCRC)

The CCRC is an integrated clinical research facility that provides clinical research expertise to UC Davis and VA investigators. The CCRC is a collaboration between the UCDHS and the Veterans Affairs Northern California Healthcare System (VANCHCS). The CCRC is located in an 8,000-square-foot area on the fourth floor in the inpatient tower at the Sacramento VA Medical Center at Mather. The nine-bed facility consists of three double and three single-patient rooms, a designated metabolic kitchen, a core laboratory, a body composition unit, videotaping facilities and offices for biostatistics, informatics administrative staff. In addition, the center has all the resources required for an inpatient facility, including a communication center, utility rooms, diagnostic area, storage facility and patient day room. The patient rooms are flexibly designed to allow for inpatient and outpatient activities. The CCRC has 10 highly skilled nurses who provide 24/7 care to subjects enrolled in clinical research studies, whether they be admitted to the CCRC, to any Health System site (i.e., the UC Davis Medical Center, any of the clinics, the MIND Institute, the Cancer Center, the Shriner’s Hospital, or a research site on the UC Davis campus, a community site, or in the home), a nurse practitioner, an exercise physiologist, a research dietitian, lab support, and clinical research coordinators. Resources include unique facilities and equipment, as well as highly experienced staff who are trained in human subjects’ protection, good clinical practices (GCP), protocol implementation and compliance.
The CCRC is planning an outpatient facility on the UC Davis Health System campus and is slated to open in the fall/winter of 2013. For more information on the facilities and availability, refer to the web address below.

For more information see [http://www.ucdmc.ucdavis.edu/ctsc/area/crc/index.html](http://www.ucdmc.ucdavis.edu/ctsc/area/crc/index.html)

**Research Ethics**
The Research Ethics Consultation Service is a free service available to all biomedical researchers at UC Davis who seek advice regarding ethically complex aspects of their biomedical research. See Clinical Trial Newsletter v7, October 2011 at [http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/](http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/)

**Community Engagement**
The Community Engagement Consultation Service provides opportunities for researchers and community members interested in healthcare research to get expert feedback on how to engage communities around research ideas, proposals, evaluations, and ongoing projects.

For more information, see: [http://www.ucdmc.ucdavis.edu/ctsc/area/engagement/index.html](http://www.ucdmc.ucdavis.edu/ctsc/area/engagement/index.html)

**2.2 Request Access to PHI Data for Preparatory Research**
If it is necessary to access identifiable patient data to determine if a research project is feasible, you must submit a Preparatory Research Application prior to reviewing any records. Upon approval, you will be authorized to access data for study feasibility purposes. The application can be found on the Compliance website: [http://www.ucdmc.ucdavis.edu/compliance/guidance/privacy/resprep.html](http://www.ucdmc.ucdavis.edu/compliance/guidance/privacy/resprep.html)

Clinical Trials Newsletter (v.12, 2012) describes access to PHI and reporting responsibilities (“information Privacy in Research”). [http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/](http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/)

**2.3 Execute Non-Disclosure Agreement**
This activity is required for industry- initiated and industry- sponsored clinical studies. In many 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/clinicaltrialscontracts/](http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/)). HS Contracts–Clinical Trials reviews CDAs in great detail and ensures that it complies with the University rules for confidentiality, data retention and information ownership. UC Davis PIs are highly discouraged from signing the CDAs themselves, because it puts confidentiality obligations on them personally. Individual confidentiality agreements are not required by all Sponsors, because some Sponsors may already have Master Confidentiality Disclosure
Agreements with the University. See Activity #6 of this Guidebook for other industry contracts related activities.

2.4 Create a Monitoring Plan

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).

Typically, academic sites are familiar with monitors assigned by a sponsor or a contract research organization (CRO). However, GCP requires that investigator-initiated trials enrolling human subjects also provide a monitoring plan to assure that the data collected throughout the study are accurate. In addition, the Code of Federal Regulations requires monitoring under 21CFR 312 subpart D (for INDs) and 21CFR 812 subpart C (for IDEs). Sponsors (including Sponsor-Investigators) of clinical investigations conducted under an IND or IDE are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data submitted to FDA. This oversight is maintained through the regular review of the source data, case report forms, informed consents, regulatory documents, and any other essential documents by a monitor.

During a monitoring visit, a monitor reviews individual subject records and source documents, regulatory binder(s), and other essential documents and compares the information with data recorded on the case report forms (CRF) or entered in the electronic case report form (eCRF). The monitor is obligated 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 the trial is in compliance with protocol, good clinical practice (GCP), and applicable regulatory requirements.
- Subjects are 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 must be accurately recorded on the CRF.
- The CRF is complete, legible, and consistent throughout visits.

For further information on what is involved in monitoring, see the presentation “What to expect during a monitoring visit” at http://intranet.ucdmc.ucdavis.edu/ctsc/area/cttraining/index.shtml

Typically, in an industry-sponsored study, the pharmaceutical company will provide the monitor for the study. However, in the case of a study conducted by a Sponsor-Investigator, the Investigator takes on the responsibility of ensuring that the study is being monitored.
For Industry sponsored studies a monitoring plan will often be used to guide the frequency of monitoring visits to investigative sites, whereas in an Investigator-initiated study the Investigator and/or study staff should develop a monitoring plan. The frequency of visits is affected by the complexity of the study and the rate of enrollment. Monitoring plans can be updated during the course of the study if, for example, enrollment is faster than expected.

When a monitor comes to a clinical site to conduct a monitoring visit, he/she will need access to all source documents, including the Electronic Medical Record (EMR). At UCDHS, Physician Connect is the system that provides monitors access to the EMR in a read-only format. The monitors will only have access to the records of those patients who are enrolled in the study. For more information and directions on how this process works please see the January 2013 Clinical Trials Newsletter at http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/

2.4.1 CTSC Monitoring and Quality Assurance Program

The CTSC Clinical Trial Resource Group Monitoring and Quality Assurance Program provides both monitoring and auditing on an as needed basis. The program is offered to all investigator initiated studies that otherwise are not monitored/audited by another entity. The program aims to provide a proactive (as opposed to “for cause”) regulatory assessment of a study in order to preclude the development of non-compliance situations. The program also helps with preparation for the FDA and sponsor audits. The services are provided at no cost for unfunded studies. The recharge rates for funded studies are negotiated on an individual basis.

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 Resources Group for details http://www.ucdmc.ucdavis.edu/clinicaltrials/Monitoring/index.html.

2.4.2 Establish a DSMB/C (if required)

This section discusses the roles, responsibilities and operating procedures of Data Monitoring Committees (DMCs) (also known as Data and Safety Monitoring Boards (DSMBs) or Data and Safety Monitoring Committees (DSMCs)) that may carry out important aspects of clinical trial monitoring.

A clinical trial Data Monitoring Committee is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DMC advises the investigator regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.
DSMC/Bs have the practical position of seeing data and safety information in more frequent intervals and with typically more statistical expertise to make enhanced assessments about a study’s progress and determine the study’s future.

**DSMC/B: What do they do?**

DSMC/Bs perform the following general functions:

- Objectively appraise a study’s progress
- Assess data quality via a formal and planned process
- Provide analytical expertise and rigor
- Determine the statistical significance of efficacy and/or risk-benefit ratio
- Serve as “Another set of eyes”

In accordance with its analytic and ethical responsibilities, a DSMC is tasked to determine whether a study can proceed with enrollment, as designed. It has the authority to halt a study, suspending enrollment, pending crucial changes to the protocol’s design, recruitment strategy, risk minimization, or other modification. It can also terminate a study due to statistically significant efficacy or increased risk of harm to participants.

**DSMC/B: When are they needed?**

A fundamental reason to establish a DMC/B is to enhance the safety of trial participants in situations, in which safety concerns may be unusually high, in order that regular interim analyses of the accumulating data are performed. All clinical trials require safety monitoring, but not all trials require monitoring by a formal DSMC/B.

DSMC/Bs are established for large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer. DSMC/Bs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity.

Formal data and safety monitoring is also necessary to assure confidence in a study’s interim and final outcomes:

- To verify or validate efficacy and/or safety information significant to a novel therapy
- To gauge data quality to confirm the research question/ hypothesis in developing treatments
- To assess efficacy and safety when “lives and wellbeing depend on valid results”
The FDA recommends that sponsors consider using a DSMC/B when:

- The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion;
- There are a priori reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;
- There is prior information suggesting the possibility of serious toxicity with the study treatment;
- The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity;
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint;
- The study is large, of long duration, and multi-center.

In studies with one or more of these characteristics, the additional oversight provided by a DSMC/B can further protect study participants. In other studies, such as short-term studies for relief of symptoms as noted above, such committees are generally not warranted. [FDA Guidances: The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors - Guidance for Clinical Trial Sponsors - Establishment and Operation of Clinical Trial Data Monitoring Committees](http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm)

**DSMC/B: Charter**

DSMC/Bs typically operate under a written charter that includes well-defined standard operating procedures. Such charters are important for the same reason that study protocols and analytical plans are important—they document that procedures were pre-specified and thereby reduce concerns that operations inappropriately influenced by interim data could bias the trial results and interpretation. The sponsor may draft this charter and present it to the DSMC/B for agreement, or the DSMC/B may draft the charter with subsequent concurrence by the sponsor. Topics to be addressed would normally include a schedule and format for meetings, format for presentation of data, specification of who will have access to interim data and who may attend all or part of DSMC/B meetings, procedures for assessing conflict of interest of potential DSMC/B members, the method and timing of providing interim reports to the DSMC/B, and other issues relevant to committee operations. FDA may request that the sponsor submit the charter to FDA well in advance of the performance of any interim analyses, ideally before the initiation of the trial (see 21 CFR 312.23(a)(6)(iii)(g); 21 CFR 312.41(a); 21 CFR 812.150(b)(10)). In such cases, FDA would usually consider the charter when FDA reviews the study protocol. [FDA Guidances: The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors - Guidance for Clinical Trial Sponsors - Establishment and Operation of Clinical Trial Data Monitoring Committees](http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm)
2.5 Complete Radiology Research Procedure Request Form

The Department of Radiology supports and encourages clinical research at UCDMC. If your protocol contains radiology services, it is highly advised that you communicate with the Department of Radiology prior to starting your study or even at the protocol preparation step. Radiology will establish the exact process for your procedure and will provide cost estimate. This is especially important if your experimental requirements deviate from the standard radiology procedures, i.e. require an unusual contrast agent. It is not uncommon that radiology services are not clearly detailed in the text of the protocol, potentially resulting in additional unanticipated charges at the point of service.

All research protocols/studies that involve non-routine imaging studies, e.g. studies involving modified acquisition, processing, analysis, display, and/or storage, must be reviewed and approved prior to study initiation.

What to submit to the Radiology:
1. Research protocol
2. Research Procedure Request Form
   a. Check box “Preparatory Research”
   b. Fill only sections 1-10a
   c. Signatures are not required

Send to:
Desirée Lazo
Administrative Research Coordinator, Department of Radiology,
4860 Y Street, ACC, Suite 3100; Sacramento, CA 95817
desiree.lazo@ucdmc.ucdavis.edu
Phone: (916)734-3651

The Research procedure Request Form and Instructions may be found at:
http://intranet.ucdmc.ucdavis.edu/researchbudgeting/tracking/index.shtml

2.6 Contact Pathology Client Services (Lab)

UC Davis Health System Department of Pathology and Laboratory Medicine is fully accredited by the College of American Pathologists (CAP), licensed by the State of California, the Clinical Laboratory Improvement Act (CLIA), Foundation for the Accreditation of Cellular Therapy (FACT), and American Association of Blood Banks (AABB). It performs over 3,000 tests. To find what tests is offered by the department of Pathology, please see Laboratory Test Directory, accessible only via intranet (http://www.testmenu.com/public/cltdLaunch.aspx).
Laboratory Licenses (such as CLIA) and Accreditations can be found here: http://www.ucdmc.ucdavis.edu/pathology/services/clinical/licenses/

Anatomic Pathology provides autopsy, cytopathology, neuropathology and surgical pathology. Clinical Pathology provides apheresis, hematopathology, molecular/Cytogenetics, Point of Care Testing and Transfusion Medicine. It also includes UC Davis Medical Center Clinical Laboratory, a full-service anatomic and clinical pathology laboratory, offering one of the most extensive routine and esoteric testing menus in and beyond the Northern California region.

Some of the pathology services may require additional information prior to receiving the specimen. This is especially important for microbiology samples, that may need to grow for a period of time under certain lab conditions. To ensure that your clinical trial protocol specimens are processed correctly and in the timely manner, please contact Pathology Client Services at (916) 734-7373, option1, or Letitia Lafforday (916-734-7597) prior to beginning of your study.

Fill out the Research Checklist and FAX to the Client Services.

For blinded studies, where results of laboratory testing are not recorded in the EMR, complete Secured Fax and Secured Print Forms. Obtain the Requisition Form from Pathology Client Services, fill it out (a Bulk Account number is required). This
requisition MUST accompany the sample to the laboratory. Forms can be found on Clinical Trials website – Tools for Study management http://www.ucdmc.ucdavis.edu/clinicaltrials/StudyTools/StudyTools.html

For studies, where results are released into the EMR, follow the Lab Process Map and Activity # 9 of this Guidebook.
http://intranet.ucdmc.ucdavis.edu/researchbudgeting/tracking/index.shtml

2.7 Contact Investigational Drug Services

See Activity 10 for detailed description of the Investigational Drug Services (IDS), start-up requirements and fees.
ACTIVITY #3: IND and IDE Submissions

3.1 Regulatory Requirements for New Drugs, Biologics or Dietary Supplements

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.

A drug is defined as:

a. article intended for use in diagnosis, cure, mitigation, treatment, or prevention of the disease;
b. articles (other than food) intended to affect the structure or any function of the body;
c. articles intended to be used as components of any of the above.

Below is a brief summary of regulatory requirements for clinical research involving drugs, biologics or dietary supplements.

3.1.1 Preclinical Regulatory Requirements

Preclinical testing begins after a potential drug has been identified in the lab. 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), 21 CFR 58. 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. Please see “Roadmap for Academic Health Centers to Establish Good Laboratory Practice-Compliance Infrastructure”, Acad. Medicine, 2012 87(3):279-284

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 and 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 two weeks to three 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; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074980.pdf).

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

After preclinical testing is completed, a sponsor or sponsor-investigator (see below) files an IND with FDA prior to beginning any human testing. An IND is a request for 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.

Clinical Trials Resource Group houses a website that provides step-by-step guide to how to file an IND (http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/index.html). However, we highly recommend contacting Clinical Trials Group for consultation regarding INDs or IND Exemptions. The team’s qualified staff also prepares FDA filings on contractual basis.

3.1.3 Special IND Subtypes

Expanded Access of Investigational Drugs: Treatment IND (21 CFR 312.320)

A treatment IND allows patients, whose need for treatment outweighs 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 IND requires 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&P1509](#).


### 3.1.4 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. Most academic drug development efforts do not progress to this stage.

At the NDA submission stage, 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.

### 3.1.5 Determine if your Study is Exempt from IND Requirements

Many academic investigators will want to conduct a clinical study with an already approved drug. This is often done to establish efficacy in a new disease indication. FDA provides provisions for conducting studies of lawfully marketed drugs through the use of an IND exemption. A clinical investigation of a drug is exempt from the IND requirements if *all* of the criteria for an exemption in 21CFR312.2(b) are met:

1. The investigational drug is lawfully marketed in the United States
2. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use of the drug product
3. The investigation is not intended to support a significant change in advertising to an existing lawfully marketed prescription drug product
4. *The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.*
5. The investigation will be conducted in compliance with the requirements for institutional review set forth in FDA regulations 21 CFR 56, and requirements for informed consent as set forth in FDA regulations 21 CFR 50
6. The investigation will be conducted in compliance with FDA regulations 21 CFR 312.7: Promotion and charging for investigational drugs.

Thorough documentation is required to support this exemption criterion 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.*


### 3.1.6 Is 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 for the purposes of this study.
ACTIVITY #3

The study will be the subject to the same regulations as any other unapproved drug. Specifically, the FDA will be paying particular attention to the composition of the dietary supplement, its origin and manufacturing processes. When preparing an IND for a dietary supplement, make sure that the supplement manufacturer is willing to provide this information.

3.2 Learn about the regulatory requirements for clinical studies with devices

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.

If a product is labeled, promoted or used in a manner that meets the 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 the Division of Small Manufacturers, International and Consumer Assistance (DSMICA) can assist in making a determination.

3.2.1 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, Class II and Class 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 Class III.

Device classification depends on the intended use of the device and also upon indications for use. In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Examples:

- **Class I**: elastic bandages, examination gloves, and hand-held surgical instruments.
- **Class II**: powered wheelchairs, infusion pumps, and surgical drapes.
- **Class III**: 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 determine the classification of 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 ([http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf)). 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 applicable regulatory requirements. 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. The FDA’s Device Advise (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm) is an excellent regulatory assistance resource.

3.2.2 Significant Risk vs Non-significant Risk Device

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

A 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 studies do 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. Significant risk devices require submission of an investigational device exemption (IDE) to CDRH (see below).

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.

FDA guidance document Significant Risk and Non-significant Risk Medical Device Studies can be used to help classify a device (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf).
3.2.3 Investigational Device Exemption (IDE) (21 CFR Part 812)

IMPORTANT: a clinical study of a new indication for an already marketed device falls under the IDE regulation.

Depending on the characteristics of the investigational device and the protocol, investigations of devices fall into one of three categories: exempt, studies of non-significant risk devices subject to abbreviated IDE requirements, or significant risk devices subject to full IDE requirements. 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.

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.


3.2.4 Abbreviated IDE

Studies of non-significant risk devices are subject to abbreviated IDE requirements. An IDE submission to the FDA is not required under the abbreviated requirements, but the requirements for labeling, informed consent, monitoring, records and reports, and promotional practices contained in FDA regulations still apply (21 CFR 812.2(b)). In addition, the concept of “non-significant risk” to determine whether abbreviated IDE procedures are appropriate should not be confused with “minimal risk” to determine whether expedited IRB review is appropriate. For a device study to be eligible for expedited IRB review, it must be a non-significant risk device AND present no more than minimal risk to the subject (ref. 21 CFR 56.110).

Requirements under abbreviated IDE (see appendix 2 for more details):

- The device is not a banned device;
- The sponsor will label the device in accordance with 21 CFR 812.5;
• The sponsor will obtain IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
• The sponsor will ensure that each investigator participating in an investigation of the device obtains from each subject under the investigator’s care consent under 21 CFR 50 and documents it, unless documentation is waived;
• The sponsor will comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
• The sponsor will maintain the records required under 21 CFR 812.140(b) (4) and (5) and make the reports required under 21 CFR §812.150(b) (1)-(3) and (5)-(10); The sponsor will ensure that participating investigators will maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7);
• The sponsor will comply with the prohibitions in 21 CFR 812.7 against promotion and other practices.

3.2.5 IDE Exemptions

Some studies may be exempt from the IDE regulations. The exemption criteria is explained in 21 CFR 812.2(c), and briefly summarized below:

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

3.2.6 Emergency Use of Unapproved Device

If this situation is encounter, act in accordance with UCDMC P&P 1509. “Emergency Treatment of an Investigational Drug, Device or Biologic (FDA Regulated Products) in a Life Threatening Situation.”
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).

3.2.7 Compassionate use of Investigational Devices

*This type of use is NOT an emergency use.* Compassionate use request to utilize an investigational device in the mitigation, diagnosis and treatment of a serious disease requires an IDE Supplement. The sponsor or investigator has to submit the protocol for 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

3.2.8 Treatment Use

*This type of use is NOT an emergency use.* A request for Treatment Use of an investigational device in the mitigation, diagnosis and treatment of a serious disease 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

### 3.2.9 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 medical devices. Due to the level of risk associated with Class III 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.

### 3.2.10 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) or to the Center for Biologics Evaluation and Research (CBER). 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” [http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/DesignatingHumanitarianUseDevicesHUDS/LegislationRelatingtoHUDsHDEs/ucm283517.htm](http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/DesignatingHumanitarianUseDevicesHUDS/LegislationRelatingtoHUDsHDEs/ucm283517.htm).

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.

3.3 Learn about Investigators, Sponsors, and Sponsor-Investigators

**Investigator** means 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).

**Sponsor** means a person who takes responsibility for and initiates a clinical investigation (21CFR312.3). The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation.

**Sponsor-Investigator** means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed (21CFR312.3). The term does not include any person other than an individual. If an academic investigator submits an IND or IDE and is the principal investigator, the investigator is the Sponsor-Investigator and he/she is responsible for regulatory compliance.

Academic investigators sometimes equate the term “Sponsor” with the 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.

A financial sponsor may be a company, a department, a non-profit or a government agency. If a pharmaceutical (or device) company is supplying a drug (or device) for an academic study, but will not be submitting the IND or IDE, the company is not the regulatory sponsor. For commercial INDs, the financial and regulatory sponsors are usually the same (i.e. the pharmaceutical or device company).
Helpful delineation of the ownership of the study processes (adapted from the UCOP Office of General Counsel):

<table>
<thead>
<tr>
<th>Issue</th>
<th>Sponsor-initiated study</th>
<th>Investigator-initiated study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Author</td>
<td>Sponsor</td>
<td>Investigator</td>
</tr>
<tr>
<td>Holds IND/IDE</td>
<td>Sponsor</td>
<td>Investigator (or University)</td>
</tr>
<tr>
<td>Injuries and indemnifications</td>
<td>Sponsor pays (except when caused by the institution or Pi non-compliance, negligence or misconduct)</td>
<td>Institution pays (except for product defects)</td>
</tr>
<tr>
<td>Data</td>
<td>Sponsor owns CRFs and reports provided by sponsor; UC owns medical records and other data</td>
<td>UC owns protocol, documents, research results, data</td>
</tr>
<tr>
<td>IP</td>
<td>Sponsor owns patentable inventions conceived and reduced to practice; UC owns everything else</td>
<td>UC owns all inventions and IP</td>
</tr>
<tr>
<td>Funding</td>
<td>Sponsor</td>
<td>Grants, Institution, Department</td>
</tr>
</tbody>
</table>

### 3.4 Sponsor-Investigator Responsibilities


Below is a brief summary of the responsibilities and available resources for Sponsor-Investigators under an IND:
21 CFR Part 312.50 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.

For drug studies, additional specific responsibilities of sponsors are described:

§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

For device studies, additional specific responsibilities of sponsors are described:

§ 812.40 - General responsibilities of sponsors.
§ 812.42 - FDA and IRB approval.
§ 812.43 - Selecting investigators and monitors.
§ 812.45 - Informing investigators.
§ 812.46 - Monitoring investigations.

21 CFR Part 312.60 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:

§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 corresponding onsite documents can be found at [http://www.partners.org/phsqi/ToolsPage.htm](http://www.partners.org/phsqi/ToolsPage.htm)

See [http://www.ucdmc.ucdavis.edu/clinicaltrials/Training/2013ctcalendar.html](http://www.ucdmc.ucdavis.edu/clinicaltrials/Training/2013ctcalendar.html) for a detailed presentation of Sponsor-Investigator responsibilities under an IND.

### 3.5 Request Assistance from CTSC Clinical Trials Resource Group for IND/IDE Preparation


### 3.6 Submit IND/IDE to the FDA


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).
**ACTIVITY #4: Prepare Documents**

### 4.1 Financial Approval

#### 4.1.1 Review CTSC SOP # 4, #5, #6, #7, #8, #9

The purpose of these SOPs is to provide guidance to research personnel on how to complete a clinical trial Coverage Analysis, budgets, and to receive institutional and Departmental approvals. Reference: [http://intranet.ucdmc.ucdavis.edu/ctsc/area/c clinicaltrials/processmaps.shtml](http://intranet.ucdmc.ucdavis.edu/ctsc/area/c clinicaltrials/processmaps.shtml)

#### 4.1.2 Complete Coverage Analysis

**Clinical Research Billing**

Clinical research billing compliance has become a major focus area of compliance professionals in recent years. Clinical research is highly regulated by federal regulations and state laws, as well as IRBs. The Research Billing Compliance Program at UCDHS was developed to ensure appropriate billing practices for covered versus non-covered services related to research protocols approved by the Institutional Review Board (IRB). The program performs reviews of selected protocols for accurate regulatory and billing practice activity. This review process ensures that research costs are accounted for and billed appropriately according to the research study documents.
The Centers for Medicare and Medicaid Services (CMS) 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. Medicare coverage for clinical trials is limited to items and services that are reasonable, 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.

CMS Medicare contracts with local intermediaries to administer the Medicare Program. As of August 2013, the local Medicare contractor (intermediary) for California is Noridian. 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 (Noridian). Specific claims processing instructions can be found in the Medicare Claims Processing Manual and in the NCD 310.1.

If your study enrolls patients on the **Medicare Advantage Plan**, be aware of special requirements for copays and claims processing. For updated information on the Medicare Advantage Plan research billing guidelines, see the Clinical Trials Newsletter v9, June 2012 [http://intranet.ucdmc.ucdavis.edu/ctsc/area/CTNewsletters/Documents/Newsletter%20June%202012%20final2.pdf](http://intranet.ucdmc.ucdavis.edu/ctsc/area/CTNewsletters/Documents/Newsletter%20June%202012%20final2.pdf)

Claims filed to Medicare (and in some instances, to other insurance providers) must report special identifiers to show that the claim was issued for research-related services and procedures. These identifiers are **V70.7 diagnosis code and Q0/Q1 modifiers**. Investigators and clinical research coordinators are responsible for providing sufficient documentation in Electronic Medical Records for billers to add these identifiers to the claims. Claims that miss either V70.7 diagnosis code or “Q” modifiers may be rejected by Medicare and returned back to the study team for corrections.
For updated information on the use of “Q” modifiers in coverage analysis, see the Clinical Trials Newsletter v8, May 2012 http://intranet.ucdmc.ucdavis.edu/ctsc/area/CTNewsletters/Documents/Newsletter%20May%202012_final.pdf


**What is Coverage Analysis?**
The NCD necessitates a priori delineation of what clinical trial services/procedures can be billed to Medicare, and which can only be billed to the study. Such delineation can be expressed in a Medicare Coverage Analysis (MCA) or simply Coverage Analysis (CA).

In order to bill the third-party payors, a clinical study must meet qualifying criteria. Coverage Analysis is a process of determining when a clinical study qualifies for Medicare coverage and lists these services in a Billing Grid. The grid identifies which clinical study-related procedures and services can be paid by the third party payor, including Medicare, and which should only be paid by the study sponsor. At UC Davis Medicare coverage criteria are used and extended to all insurance companies. Insurance policies vary in their coverage of clinical studies; 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 Trial SOP #4 (http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml).

A Coverage Analysis is mandatory for all studies that include billing of patient care services in the UC Davis Health System. The Principal Investigator is ultimately responsible for ensuring that the Qualifying Clinical Trials (QCT) Form and Billing Grid (which together make up the Coverage Analysis) are accurate. Both forms must be approved and signed by the principal investigator. The Department will store a paper or electronic copy on file (in the Study Financial Binder) for audit purposes.

**Coverage Analysis is required prior to IRB submission (CTSC SOP#4).**

**Qualification Process**
The first step in Coverage Analysis is determining if a study qualifies. This is a process for principal investigators to attest to Medicare that a clinical study meets certain Medicare qualifying criteria. When the study meets this criterion, it is a “qualifying clinical trial.” This means that Medicare (and by extension, other
insurance companies) will cover associated routine and expanded patient care during the clinical study. Routine care is also called “standard of care” and defines procedures/services that would be performed absent a clinical study. Expanded care includes additional services such as clinically necessary monitoring of the effects the investigational drug or device, administration of the clinical study article (drug or device), procedures for prevention, diagnosing, and treatment of side effects or complications resulting from the patient’s participation in the clinical study (Medicare Clinical Trial Policy, NCD 310.1).

Medicare will not cover items and services that are paid for by the sponsor, promised free in the informed consent document, not ordinarily covered by Medicare, and studies that are solely for data collection or analysis.

<table>
<thead>
<tr>
<th>What types of services are covered in a clinical trial?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Qualified Trial</strong></td>
</tr>
<tr>
<td>Conventional care (SOC)</td>
</tr>
<tr>
<td>Services to monitor effects of investigational drug/device</td>
</tr>
<tr>
<td>Services to administer investigational drug/device (e.g. infusions, surgery)</td>
</tr>
<tr>
<td>Services to prevent, diagnose, and treat complications</td>
</tr>
<tr>
<td>Protocol related services and items must be billed with clinical trial modifiers and diagnosis codes for Medicare patients</td>
</tr>
</tbody>
</table>

Information about the qualification process can also be found in the Clinical Trials Newsletter v3, June 2011 [http://intranet.ucdmc.ucdavis.edu/ctsc/area/CTNewsletters/Documents/Newsletter_June_2011_final.pdf](http://intranet.ucdmc.ucdavis.edu/ctsc/area/CTNewsletters/Documents/Newsletter_June_2011_final.pdf)
Device Trials

CMS determines Medicare coverage of devices based on which category the FDA assigns the device. Devices are either designated as a Category A IDE or a Category B IDE.

Providers that participate in an IDE trial and anticipate filing Medicare claims must notify the Medicare contractor. The following information must be furnished prior to submission of a claim for payment:

- A copy of the FDA-approval letter provided to the sponsor or manufacturer of the device. The approved IDE number must be on the letter;
- The name of the device (both trade, common or usual, and classification name);
- Any action taken to conform to any applicable IDE special controls;
- A narrative description of the device sufficient to make a payment determination;
- A statement indicating how the device is similar to and/or different from other comparable products;
- Indication of whether the device will be billed on an inpatient or outpatient claim;
- A brief summary of the study design or a copy of the actual trial protocol;
- The provider’s protocol for obtaining informed consents for beneficiaries participating in the clinical trial.

A device flowchart detailing the process for filing for Medicare approval of devices is located in the Coverage Analysis section on the CTSC webpage (http://intranet.ucdmc.ucdavis.edu/researchbudgeting/coverageanalysis/index.shtml). For assistance in this process contact Suzan Bruce suzan.bruc@ucdmc.ucdavis.edu

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 policies. Many hospital procedures, especially surgical and laboratory procedures, may contain multiple “bundled” codes. Without identifying all bundled codes, it may not be possible to estimate true cost of the procedure. Use Coverage Analysis Checklist to identify potential “hot spots” for bundled codes.
A “Preliminary Billing Grid” is prepared based on the Medicare and billing policies. A CTSC Coder will help to analyze the protocol to identify all billable services. In the case of industry-sponsored studies, a sponsor may decide to pay for a service/procedure regardless of Medicare rules. This should be reflected in a Clinical Trials Agreement and the negotiated budget. Once the budget is approved and the CTA is signed, the Billing Grid for this study should be updated to reflect the changes. At this point, it is called “Final Billing Grid.” In contrast, investigator-initiated studies funded by a grant or department funds only have one version of billing grid, “Preliminary.”

Note that the Billing Grid needs to include the study objective. This statement is important to support qualification of the trial.

See Clinical Trials Newsletter v 9, June 2012 for further information
http://intranet.ucdmc.ucdavis.edu/ctsc/area/CTNewsletters/Documents/Newsletter%20June%202012%20final2.pdf

Coverage Analysis documents, including the Qualifying Clinical Trials (QCT) Form, Checklist and a template of the Billing Grid, are located on the Clinical Translational Science Center (CTSC) website http://www.ucdmc.ucdavis.edu/clinicaltrials/BudgetingBilling/index.html

4.1.3 In-Service Clinical Research Coverage Analysis and Billing

In-Service training for Coverage Analysis provides research staff with hands on instructions and application of the Coverage Analysis process based on the specific needs of the department. Training sessions include an overview of the Coverage Analysis requirements and how to complete the Qualifying Clinical Trials (QCT) Form and Billing Grid. It also includes information on the requirements listed in the Medicare National Clinical Trials Policy, tools available on the CTSC website for developing the Coverage Analysis, and guidance on the existing policies and procedures related to clinical trial billing.

For scheduling, contact Suzan Bruce suzan.bruce@ucdmc.ucdavis.edu

4.1.4 Prepare and negotiate budget for Industry-Funded Studies

Complete Internal Budget

A preliminary Billing Grid based on the Medicare medical policies is a foundational document for a sound budget for both industry- and investigator-initiated studies.
The Internal Budget identifies study costs based on labor costs and research rates for procedures as identified in the Coverage Analysis Billing Grid. UC Davis uses the Excel template called the Unified Budget Template [http://intranet.ucdmc.ucdavis.edu/researchbudgeting/budgeting/index.shtml](http://intranet.ucdmc.ucdavis.edu/researchbudgeting/budgeting/index.shtml).

The template consists of following components:

1. Start-up Costs
2. Close-out Costs
3. Invoicable costs (yearly or per occurrence)
4. Per patient costs

The first three categories are based on the anticipated time and expense to conduct these activities. The template provides time brackets as a guideline. Per patient costs are composed of protocol-related procedures and hospital services. Only those hospital procedures and services that are not paid by insurance will be included in the internal budget. To determine what is payable by the study and what is payable by insurance, refer to the Coverage Analysis and incorporate correct line items in the per-patient grid. Once internal costs are estimated, use this as a reference to negotiate the external budget with the study sponsor. The final contract budget will reflect the negotiated rates that the sponsor will pay.

**Negotiate the External Budget with Industry Sponsor**

External budgets are negotiated with Industry Sponsors based on the going market rate. The external budget should be equal to or exceed the internal budget. Formats for these budgets may vary, as different sponsors may require their own formats. External budgets are often expressed as “per patient cost.” Only projects that meet a “clinical trial” definition may be negotiated at HS Contracts with 26% overhead rate. If it is not clear as to whether the project meets the definition of a clinical trial, contact Health System Contracts–Clinical Trials Office prior to budget negotiations ([http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/](http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/)).

As of the time of the publication, the PI is responsible for preparing a preliminary internal cost budget, negotiating a final (external) sponsor budget and submitting to the Department Chair for signature. The negotiated budget will become part of the contract packet, submitted to the SOM Dean’s Office for approval and forwarded to HS Contracts-Clinical Trials. There the Budget Analyst will review for policy compliance and approve the final internal cost budget. Because of anticipated changes to this process, please follow the most recent guidance on CTSC Clinical Trials website.
4.1.5 Prepare Budget for Grant or Department Funded Studies

This process pertains only to those studies that involve patient care services at UC Davis Hospital and Clinics.

Once the research team develops the description of the study (clinical trial protocol), it is strongly encouraged that the team contacts CTSC Clinical Trial Resource group. CTSC will provide analysis of the protocol to ensure compliance with clinical research billing requirements and prepare correct budgets for patient care costs and other research activities. The CTSC Clinical Trial Resource group will provide analysis of:

- **The billing grid of patient care services/procedures** involved in the protocol (called Coverage Analysis). Analysis of these services and which procedures may be billed to insurance during the clinical trial is essential and required at the time of IRB submission. A CTSC Clinical Research Billing Analyst will prepare the Coverage Analysis (CA) document to delineate items that can be billed to Medicare or another third party payer versus those that are not covered by the insurance and must be paid out of the study budget. Understanding of clinical research billing ensures correct budgeting to account for hospital/clinical charges.

- **Hospital/Clinic Costs** for study-related procedures and services that are not covered by insurance and therefore must be paid by study budgets. CTSC Analyst will help to assess the cost based on the completed CA. Costs are also available from CTSC Budgeting and Billing website (http://www.ucdmc.ucdavis.edu/clinicaltrials/BudgetingBilling/index.html).

- **Operational Feasibility** to assess potential scheduling conflicts, operating room availability, radiology research procedures, IDS pharmacy role, microbiology research procedures, etc.
• **Regulatory Assessment** of trial activities required to comply with FDA, ICH GCP, IRB, and Medicare regulations. This may include assessment for regulatory compliance, and data quality monitoring and quality assurance support.

• **Other Clinical Trial Expenses** such as fees for language translation, investigational drug pharmacy, shipping, sample and record storage, and advertising. Use the worksheet in CTSC SOP#6 as guidance to identify other possible items that have budgetary implications.

The CTSC Clinical Trial Resource group will prepare a proposal to summarize the assessment and to detail the potential costs of services recommended. Please note that The CSTC analysis will not replace the budgets as required by the granting agency guidelines. It is to be used as an estimate only and does not represent commitment of funds or resources.

The Unified Budget Template is not used for grant and department funded studies. However, the costs identified by CTSC need to be included in budgets prepared in accordance with a granting agency guidelines. For department sponsored studies, CAO and the Chair need to agree to expend funds for clinical trial costs as identified by CTSC.

For more details, see: CTSC SOP #6 [http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml](http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml).

4.1.6. **Subject Injury and Complications**

While the 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 are considered.

For privately sponsored studies (*industry sponsor*), the sponsor of the study is required to pay for injuries/complications **directly** attributable to 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 (UC Operating Requirement 95-05). Other costs that occurred during conduct of the study but not directly attributable to the subject’s participation (i.e. typical for this type of disease or procedure) may be billed to the insurance. In some cases, determination of whether the complication was directly or indirectly related may not be clear.
Example:

If an investigational medication is administered via an intravenous infusion, and the needle entry site became infected, it does not necessarily mean that this injury is directly related to the investigational drug administration. Other factors need to be considered. If the standard of care or alternative treatment is oral medication, then the i.v. infection may be directly attributed to the investigational study drug. However, if the standard of care treatment is also intravenous, then the infection maybe construed as being a consequence of this typical intravenous procedure, and therefore, no directly related to the investigational drug administration.

Contact UC Davis Risk Management risk.management@ucdmc.ucdavis.edu or (916) 734-3883 for help with determination.

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 some instances it still may be appropriate to bill Medicare/private insurance, and in some cases, the UC Human Subject Injury Program may cover these costs. Contact Risk Management as directed above.

4.2 Regulatory Approval

4.2.1 Read IRB SOPs and the Investigator Manual

The UC Davis IRB Investigator Manual (HRP-103) provides a wealth of information about the IRB at UC Davis. It is advisable that you consult this document prior to preparing your application http://research.ucdavis.edu/c/cs/hrp/documents/HRP103INVESTIGATORMANUAL.docx

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.

Types of regulatory determinations for research activities

Submitted research activities may fall into one of the following four regulatory classifications:

- **Not “Human Research”**: Activities must meet the organizational definition of “Human Research” to require IRB oversight. Activities that do not meet
this definition are not subject to IRB oversight or review. Review the IRB “WORKSHEET: Human Research (HRP-310)” (http://research.ucdavis.edu/f/f#Forms-IRBAadmin) for reference. Contact the IRB Office in cases where it is unclear whether an activity is Human Research.

- **Exempt:** Certain categories of Human Research may be exempt from regulation but require IRB determination. It is the responsibility of the organization, not the investigator, to determine whether Human Research is exempt from IRB review. Review the IRB Administration’s “WORKSHEET: Exemption Determination (HRP-312)” for reference on the categories of research that may be exempt.

- **Review Using the Expedited Procedure:** Certain categories of non-exempt Human Research may qualify for review using the expedited procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review the IRB Administration’s “WORKSHEET: Eligibility for Review Using the Expedited Procedure (HRP-313)” for reference on the categories of research that may be reviewed using the expedited procedure.

- **Review by the Convened IRB:** Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

### Criteria for IRB Approval

In order to evaluate and potentially approve human subjects research, the UC Davis IRB must review the protocol and determine that all of the federal requirements for approval, as outlined in 45 CFR 46.111(a)(1-7)(b), are satisfied. The criteria for IRB approval can be found in the “WORKSHEET: Criteria for Approval and Additional Considerations (HRP-314)” for non-exempt Human Research. The worksheet references other checklists that might be relevant. All checklists and worksheets can be found on the IRB web site.

### What are the decisions the IRB can make when reviewing proposed research?

The IRB may approve research; require modifications to the research to secure approval, deferred, or disapprove research:

- **Approval:** Made when all criteria for approval are met. See “Criteria for IRB Approval” above.

- **Modifications Required to Secure Approval:** Made when IRB members require specific modifications to the research before approval can be finalized.

- **Tabled:** Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. When taking this action, the IRB automatically schedules the research for review at the next meeting.

- **Deferred:** Made when the IRB determines that the board is unable to approve research and the IRB suggests modifications the might make the research
approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.

- **Disapproval:** Made when the IRB determines that it is unable to approve research and the IRB cannot describe modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

### 4.2.2 Prepare IRB Packet

**Application for Initial Review** (HRP-211) [http://research.ucdavis.edu/f/f#Forms-IRBAadmin]

<table>
<thead>
<tr>
<th>HRP Form 211-Application for Initial Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRP Form 211 is the application form used for a new submission to the IRB. In addition to the items described below, form 211 has three appendices that may or may not be relevant to your study:</td>
</tr>
</tbody>
</table>

**Appendix A:** External Sites – complete for each external site at which the investigator will conduct or oversee the protocol – requires Site Name; Site Contact Name; Site Contact Phone #/email; determination if the site’s IRB will review the protocol or if the site will rely on UCD IRB.

**Appendix B:** Drugs, Biologics, Dietary Supplements, and Foods – complete by listing all unapproved drugs/biologics being used in the protocol; approved drugs/biologics whose use is specified in the protocol; foods or dietary supplements whose use is specified in the protocol. This requires information about the Generic Name; Brand Name; Package Insert or Investigator Brochure for each listed drug; whether the protocol is being conducted under an IND or not, and if so, the IND # and evidence of the IND. Acceptable evidence includes: Sponsor protocol with the IND#, communication from the sponsor documenting the IND#, or FDA approval letter indicating IND#. Information regarding the holder of the IND is also required.

**Appendix C:** Devices – complete by listing all devices being evaluated for safety or effectiveness: device Name; product labeling for each item listed; whether the protocol is being conducted under an IDE or not, and if so, the IDE # and evidence of the IDE. Acceptable evidence includes: Sponsor protocol with the IDE#, communication from the sponsor documenting the IDE# or FDA approval letter indicating IDE#. In the event that the protocol is for a Humanitarian Use Device (HUD), this same form is to be used with information regarding the HDE#.
Specific sections in HRP-211

- **Conflict of Interest Disclosure**
  The Public Health Service (PHS) regulations include new requirements for mandatory and ongoing education and training. All investigators who are engaged in any research funded by PHS agencies (including NIH) and sponsors who have adopted the PHS rules as of August 24, 2012 must complete this training prior to the receipt of any new funds from the covered entity via a Notice of Award. All investigators who will engage in research funded by a covered entity after August 24, 2012 must complete the training prior to engaging in the research following receipt of funds via a Notice of Award. Any investigator who is added to an existing research project after August 24, 2012 must complete the training prior to engaging in any research on the project.

  Provide evaluation of any related financial Interest for study personnel (need to submit the determination from the Conflict of Interest Committee (COIC) regarding conflict management if a conflict of interest does exist) (see section 4.2.2).

  In order to meet new requirements to update positive COI at least annually and not hold up IRB annual renewal, submit appropriate paperwork at least 3-4 months before IRB annual renewal is due.


- **Protocol**
  - Sponsor Protocol (Industry Sponsored Study) – entire sponsor protocol must be submitted to IRB. For any items described in the sponsor’s protocol, grant, contract, or other documents submitted with the application, include the appropriate text within the HRP-503 TEMPLATE PROTOCOL ([http://research.ucdavis.edu/f/f#Forms-IRBAdmin](http://research.ucdavis.edu/f/f#Forms-IRBAdmin))
  - Investigator Protocol (Investigator-Initiated Study) (HRP-503 TEMPLATE PROTOCOL)

- **Written materials meant to be seen or heard by subjects**
  - Evaluation instruments and surveys
  - Advertisements (printed, audio, and video)
  - Recruitment materials and scripts
  - Consent Documents
  - If consent will not be documented in writing, a script of information to be provided orally to subjects
  - Foreign language versions of the above

  As described in section 2.2, to look at protected health information (PHI) not for research purposes, but for preliminary purposes such as evaluating whether a research project is feasible or not, apply for access to the PHI under the “review prepatoratory to research” portion of HIPAA. If identified patient information is
used for recruitment purposes, how the PHI will be obtained must be described in the research protocol (Protocol Template (HRP-503). Recruitment materials specifically designed for this cohort must also be submitted to the IRB for review and approval.

- **Informed Consent**
  Create an Informed Consent Document - Use the “TEMPLATE CONSENT DOCUMENT” (HRP-502) from the IRB website.
  - If consent will not be documented in writing, a script of information to be provided orally to subjects
  - Foreign language versions of the above (if applicable), should be submitted as a modification to the IRB after initial approval.

Please be sure to use the current consent template (HRP-502) from the IRB website, as the standard UC Davis boilerplate language and formats are updated frequently. When receiving a consent form from industry sponsors, incorporate the information into the 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. In most cases, the UC Davis version of the consent form must be approved by the sponsor prior to IRB submission. The UC Davis IRB 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
6) Use of exculpatory language

**Helpful Hint: Consent versus Clinical Trial Agreement (Contract)**

<table>
<thead>
<tr>
<th>The Consent Form</th>
<th>The Clinical Trial Agreement (Contract)</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 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>It 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>
</tbody>
</table>
• **Qualifying Clinical Trials Form and Billing Grid**
  Qualifying Clinical Trials form (QCT) – required if study includes patient care services billed in the UC Davis Health System (see Activity #4 of this Guidebook).

• **Administrative Approvals Form** (HRP-226) - signed by the individuals listed in the form, including the Department Chair of the PI’s home Department. For all School of Medicine or School of Nursing studies, the Dean’s signature, of the appropriate school, is also required, and for student principal investigators (e.g., graduate students) the Faculty Advisor’s signature is required. Electronic signatures are not accepted. [http://research.ucdavis.edu/f/f#Forms-IRBAadmin](http://research.ucdavis.edu/f/f#Forms-IRBAadmin)

### 4.3 Additional Approvals

**Radiation Use Committee**
Health Physics ([http://intranet.ucdmc.ucdavis.edu/safety/hp/](http://intranet.ucdmc.ucdavis.edu/safety/hp/)) 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 that 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 Office, 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](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.

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

The Institutional Biosafety Committee (IBC) at UC Davis reviews research activities involving biological materials that may pose a risk to human, animal, or environmental health. IBC review and approval is required for research activities involving use of recombinant or synthetic nucleic acids, potential employee exposure to infectious agents, and generation of medical waste outside of clinical (patient care) environments.

Examples of research activities which may require IBC review and approval are:

- downstream uses of human blood and tissues for research purposes
- processing of patient samples for downstream research uses
- work with primary or established human cell lines
- isolation and culture of infectious disease agents
- research involving recombinant or synthetic nucleic acid molecules
- experimental uses of nucleic acids or infectious agents in human subjects
- employee exposure to any of the aforementioned activities or materials

With the exception of human gene transfer research, activities conducted in clinical environments by employees covered under established health surveillance and infection control plans do not generally require IBC review. Researchers who plan on conducting research involving use of experimental recombinant or synthetic nucleic acid technologies in human subjects are encouraged to contact the Biosafety Office at the earliest stages of their research plan for advising. If uncertain whether IBC review is required, it is always best to contact the Biosafety Office with any questions (biosafety@ucdavis.edu).

The Biological Use Authorization (BUA) is the vehicle for IBC review and authorization of research. The BUA form is available on the Safety Services website (http://safetyservices.ucdavis.edu/ps/bis/f_p/bua/bioUseAuthorization_BUA). The completed form should be submitted to the Biosafety Office via email (bua@ucdavis.edu) before the first of the month in order to be placed on the agenda for review during the IBC meeting (on the third or fourth Monday of each month). The IBC reviews BUAs according to:

- Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition (http://www.cdc.gov/biosafety/publications/bmbl5/);
- California OSHA standards 5193 (http://www.dir.ca.gov/title8/5193.html), and 5199 (http://www.dir.ca.gov/title8/5199.html) for occupational exposure to biological agents;
- hazardous waste regulations (http://www.cdph.ca.gov/certlic/medicalwaste/Documents/MedicalWaste/2013/MWMAfinal2013.pdf),

- and other guidance on best practices in biological research.

Prior to forwarding the BUA for IBC review, members of the Biosafety Office work with Principal Investigators and their representatives to complete the BUA form and application process. As part of the BUA application process, Biosafety Office staff performs audits of research locations to verify information provided in the BUA, review training records, and assess site-specific practices. Once IBC approval is granted, the BUA is active for three years with annual site audits and project reviews conducted by the Biosafety Office.

The Principal investigator (PI) is responsible for completing all required training and for ensuring their employees complete required training commensurate with tasks performed. Annual biosafety and laboratory safety training is offered through the School of Medicine and through Safety Services (http://safetyservices.ucdavis.edu/tr/biologicalSafety). Questions regarding the IBC review process or biosafety training should be directed to the Biosafety Office via email (biosafety@ucdavis.edu) or by calling the main Safety Services phone number (530-752-1493).

**Stem Cell Research Oversight Committee**

The Research Compliance & Integrity unit of the UC Davis Office of Research provides administrative support on issues pertaining to stem cell research and 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).

The Application to conduct Human Stem Cell Research can be found at: http://www.research.ucdavis.edu/f/f#Forms-%20SCRO.


SCRO SOPs are located at: 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:

- Experience with clinical research trials
- Expertise in medical, pediatric, surgical, and radiation oncology, cancer drug development, nursing, molecular biology, or data management
- Expertise in clinical pharmacology and in investigational drug requirements
- Expertise in biostatistics
- Familiarity with the UC Davis Cancer Center research base

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.

4.4 Compensation for research
The Institutional Review Board (IRB) determines whether or not the risks to subjects are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25(a)(3)]. 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, but rather a recruitment incentive. Financial incentives are often used when health benefits to subjects are remote or non-existent. 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 are coercive or present undue influence [21 CFR 50.20].

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.

For additional information see FDA’s Guidance for Institutional Review Boards and Clinical Investigators; Payment to Research Subjects – Information Sheet at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm
ACTIVITY #5: Submit to IRB and Obtain IRB Approval

5.1 Submit Required Documents to IRB

At the time of this publication, the IRB Administration accepts electronic submissions through the eDocs system, which is accessible at http://research.ucdavis.edu/edocs

The IRB plans to convert the submissions to the new electronic platform, called Kuali Coeus. Please follow the instructions as they become available on the IRB website: http://research.ucdavis.edu/c/cs/hrp

5.1.1 Submit materials to the IRB via E-Docs

Submit each document as a separate file to facilitate administrative processing. “PDF Portfolio packaging” of the submission so that each document remains as a separate file within the package is acceptable. Submissions incorporating multiple documents as a single PDF or Word document will be returned for splitting into separate documents. Missing documents can cause delays in the review and approval of a submission. If there is more than one consent form, advertisement, survey, etc., include a one to two word identifier in the footer of the document to easily distinguish the documents of the same type from each other. Document files should be named such that they are easily identifiable.

1. Go to http://research.ucdavis.edu/edocs
2. Click on “eDOCS Page”
3. Click on “Drop off your documents”
4. Enter your information in the “From:” section. [The IRB highly recommends that you utilize the drop down “Notify me of receipt,” to be informed when the document is picked up by IRB Administration staff]
5. Determine which IRB mailbox you wish drop off the documents utilizing the following descriptions:
   a. IRB Applications: use when submitting new, continuing review, modifications, closure requests, and administrative approvals
   b. IRB New Reportable Information: only use when submitting form HRP-214 “Reportable New Information”
6. Highlight by clicking once on the desired mailbox and then click “Add >>”
7. Click the “Choose File” button to browse your computer for the file you want to send. Select file, then click “Open”
8. Repeat step 7 to attach all files for a complete submission. The complete package of materials must be submitted all together through eDocs. Do not transmit one document at a time or piecemeal documents as they will not be accepted and will be deleted
9. Click “Send” to notify IRB Administration that the files are ready to be picked up through the eDocs system
10. For questions or problems, please contact IRBadmin@ucdmc.ucdavis.edu

If you inadvertently submitted an incomplete package of materials, please immediately email IRBadmin@ucdmc.ucdavis.edu.

This information can be found online at http://research.ucdavis.edu/pgc/d/irb/eDocsSubmission05.16.129.pdf
http://research.ucdavis.edu/edocs

5.1.2 Submit documents via Kuali Coeus

Follow the IRB website for instructions and training on Kuali Coeus as it becomes available (http://research.ucdavis.edu/c/cs/hrp)

5.2 Respond to IRB Comments and Obtain IRB Approval

The IRB will provide a written decision indicating that the IRB has approved the Human Research, or requires modifications to secure approval, or has disapproved the Human Research.

- If the IRB has approved the Human Research: The Human Research may commence once all other organizational approvals have been met. IRB approval is valid only for a specific period of time and has an expiration date which is noted in the approval letter.
- If the IRB requires modifications to secure approval and you accept the modifications: Make the requested modifications and submit them to the IRB. If all requested modifications are made, the IRB will issue a final approval. Research cannot commence until this final approval is received. If you do not accept the modifications, write up your response and submit it to the IRB (refer to HRP-213).
- If the IRB defers the Human Research: The IRB will provide a statement of the reasons for deferral and suggestions to make the study approvable, and give you an opportunity to respond in writing. In most cases if the IRB’s reasons for the deferral are addressed in a modification, the Human Research can be approved
- If the IRB disapproves the Human Research: The IRB will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing.

In all cases, you have the right to address your concerns to the IRB directly at an IRB meeting.

5.3 File Approvals into Regulatory Study Binder

Please reference Activity #11.8 for documentation maintenance.
ACTIVITY #6: Approval by Health System Contracts (only applicable for Industry-Sponsored Studies)

Clinical Trials Contracts negotiates industry funded clinical trial agreements for the health system (http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/)

Clinical trial agreements handled at HS Contracts office have all the following characteristics:

- Involve prospective testing in Human Subjects and always require Institutional Review Board (IRB) review (this does not include cadaver or animal studies, nor does it include retrospective chart reviews)
- Examine the efficacy, safety or benefits of a Food and Drug Administration (FDA) reviewed medical Intervention involving a drug, device, treatment or diagnostic (this would typically not include studies which involve the effects of beverages, foods or exercise on health, for example)
- Fully funded, directly or indirectly, by a for-profit entity (agreements which are partially or fully funded by non-profit, state or federal entities cannot be reviewed by this office)

Clinical Trial Packet
The department prepares the clinical trial packet and routes to the SOM Dean’s Office for approval. The complete list of forms is available online (http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/requestforms.html)
<table>
<thead>
<tr>
<th>Clinical Trial Packet</th>
<th>Section of this manual</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC Davis School of Medicine Grant/Contract Transmittal Form</td>
<td>Mandatory <a href="http://www.ucdmc.ucdavis.edu/medresearch/medsp/forms.html">http://www.ucdmc.ucdavis.edu/medresearch/medsp/forms.html</a></td>
</tr>
<tr>
<td>OVCR Data Sheet for Contract and Grant Proposals</td>
<td>Mandatory <a href="http://www.research.ucdavis.edu/pgc/d/spo/DataSource/view">http://www.research.ucdavis.edu/pgc/d/spo/DataSource/view</a></td>
</tr>
<tr>
<td>State of California Financial Disclosure Form 700-U (Statement of Economic Interests), Required for both Principal Investigators (PI) and co-PIs.</td>
<td>Mandatory, requires ORIGINAL signature (ink) <a href="http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/requestforms.html">http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/requestforms.html</a></td>
</tr>
<tr>
<td>Federal Financial Disclosure Form 800 (Statement of Economic Interests) for Government Sponsored Programs and Projects involving Human Subject Research. Required for both PI and co-PI.</td>
<td>Mandatory <a href="http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/requestforms.html">http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/requestforms.html</a></td>
</tr>
<tr>
<td>Statement of Economic Interests Supplemental Form (required if positive disclosure on 700U or 800)</td>
<td>Mandatory, if applicable <a href="http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/requestforms.html">http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/requestforms.html</a></td>
</tr>
<tr>
<td>Request for Exception to Policy on Eligibility to Submit Proposals (Form SRM 105A)</td>
<td>Mandatory, if applicable <a href="http://www.research.ucdavis.edu/pgc/d/spo/PIException/view">http://www.research.ucdavis.edu/pgc/d/spo/PIException/view</a></td>
</tr>
<tr>
<td>Feasibility Assessment (FA) At the Department’s discretion</td>
<td><a href="http://intranet.ucdmc.ucdavis.edu/researchbudgeting/budgeting/documents/STUDY%20%20FEASIBILITY%20CHECKLIST_111010.pdf">http://intranet.ucdmc.ucdavis.edu/researchbudgeting/budgeting/documents/STUDY%20%20FEASIBILITY%20CHECKLIST_111010.pdf</a></td>
</tr>
<tr>
<td>Coverage Analysis (QCT + Billing Grid) Mandatory for protocols that require billing through UCDHS Billing System (New and Amendments)</td>
<td><a href="http://intranet.ucdmc.ucdavis.edu/researchbudgeting/coverageanalysis/index.shtml">http://intranet.ucdmc.ucdavis.edu/researchbudgeting/coverageanalysis/index.shtml</a> also see section 2.8</td>
</tr>
<tr>
<td>Internal Study Budget Mandatory in Unified Budget Template (UBT) format</td>
<td><a href="http://intranet.ucdmc.ucdavis.edu/researchbudgeting/coverageanalysis/index.shtml">http://intranet.ucdmc.ucdavis.edu/researchbudgeting/coverageanalysis/index.shtml</a> also see section 2.10</td>
</tr>
<tr>
<td>Sponsor Protocol Mandatory</td>
<td></td>
</tr>
<tr>
<td>Sponsor Clinical Trials Agreement Mandatory</td>
<td></td>
</tr>
<tr>
<td>Sponsor Budgets Mandatory</td>
<td></td>
</tr>
</tbody>
</table>

**Dean’s Office Review**

The Dean’s Office School of Medicine Sponsored Programs reviews the clinical trial packet, and routes to the Health System Contracts-Clinical Trials Contracts Office (http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts). The Clinical Trials Contracts Office negotiates and has final signature authority for the agreement.
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.

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.

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.

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.

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.

Sponsor/Institutional Execution
Once approved by the PI, the contract will be sent for signature, typically starting with the PI signature of acknowledgement to the contract. After the PI signs the contract 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. However, the contract will not be awarded until the IRB has approved the project.
Contract Award
After the fully executed agreement is returned to Clinical Trials Contracts, and the IRB has approved the protocol, the HS Contracts- Clinical Trials notifies Extramural Accounting (EA). EA opens the extramural account and assigns the Office of the President (OP) fund number. This enables the Department to open the DaFIS and Bulk accounts to begin the study.

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.
**ACTIVITY #7: Study Activation**

### 7.1 Open Advance Account

If the sponsor agrees in writing (i.e., by e-mail) to provide funding for start up costs, the principal investigator can open an Advance Account. These accounts can be used to start recording your expenses early, prior to contract execution of the entire Clinical Trial Agreement. To set up the advance account, contact HS Contract-Clinical Trials Contracts. The Advance Account request form is located on the Health System Contracts webpage: [http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/requestforms.html](http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/requestforms.html)

### 7.2 Open DaFIS Account

Upon receipt of IRB approval and execution of the Clinical Trial Contract by both UC Davis and the sponsor, a DaFIS account can be opened. The HS Contracts Office notifies Extramural Accounting to set up the extramural account. Once the DaFIS (Kuali) account is set up, the financial manager or CRC opens the Bulk Account.

### 7.3 Open Bulk Account

The Bulk Account is used to place clinical study specific charges for hospital and professional patient care services. Salaries and other expenses are posted directly to the DaFIS account. Use the Coverage Analysis Billing Grid as a tool to direct and review charges billed to the Bulk Account.

To open or close your Bulk Account or change information (e.g. end date or DaFIS#), email Patient Financial Services. The Bulk Account Application Form is located on the CTSC intraweb: [http://intranet.ucdmc.ucdavis.edu/researchbudgeting/budgeting/index.shtml](http://intranet.ucdmc.ucdavis.edu/researchbudgeting/budgeting/index.shtml)

For policy on establishing a Bulk Account see Hospital Policy and Procedures # 1815 [http://intranet.ucdmc.ucdavis.edu/policies/hospital_policies_and_procedures/financial_management/1815.shtml](http://intranet.ucdmc.ucdavis.edu/policies/hospital_policies_and_procedures/financial_management/1815.shtml)

### 7.4 Post Information on clinicaltrials.gov

Clinicaltrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Title VIII of FDAAA, Public Law 110-85, amended the PHS Act by adding new section 402(j), 42 U.S.C. § 282(j). These provisions require that additional information be submitted to clinicaltrials.gov established by the National Institutes of Health (NIH)/National Library of Medicine (NLM). This includes expanded information on clinical trials and information regarding the results of clinical trials. This is a statutory requirement that applies to Investigational New Drug Applications (INDs), Biological License Applications (BLAs) and Investigational Device Exemptions.
(IDEs). The Sponsor or Sponsor-Investigator submits a certification (FDA Form 3674) attesting that the data will be submitted as available. Single patient, emergency use INDs do not fall under the referenced section, and therefore are not required to submit certification. Commercial IND/IDE sponsors are allowed to delay the data submission for commercialization purposes. Data submission by investigator-initiated studies is often dictated by the requirements of the scientific journal, where the investigator intends to publish.

Non-compliance with clinicaltrials.gov registration may result in fines up to $10,000/day.

For UC Davis-specific instructions on how to register a trial on clinicaltrials.gov, please reference http://www.ucdmc.ucdavis.edu/clinicaltrials/ClinicalTrialsGov/clinicaltrialsgov.html

Other Relevant Links
NIH Guidance on ClinicalTrials.gov Registration Requirements

ClinicalTrials.gov Protocol Registration System
http://prsinfo.clinicaltrials.gov/

7.5 File paperwork into Study Binders

See Activity #11.8 for ideas on how to organize documentation.
ACTIVITY #8: Subject Recruitment

8.1 Identify Prospective Subjects from EMR

Cohort Discovery Tool and Specific Patient Cohorts
The cohort discovery tool provides researchers the ability to query several sources of patient data. Cohort discovery is a repository of patient information gathered from multiple sources, including electronic medical records, lab results, and demographic data. Register with Cohort Discovery and take training (http://www.ucdmc.ucdavis.edu/ctsc/area/informatics/cohortdiscovery/). In order to contact patients identified by EMR screening, provide the contact script (usually a paper letter) to the IRB for review. Describe the planned approach in HRP-503, Section 25 - Recruitment Methods.

HIPAA Waiver of Authorization for Recruitment
A HIPAA Waiver of Authorization can be obtained from the IRB if access to patient data is needed for recruitment purposes. Describe the need in the protocol template (HRP-503, Section 25 - Recruitment Methods). This section is reviewed by the IRB. If a full or partial waiver is granted, access to identifiable patient data to determine if a patient may be a potential research subject will be authorized. IRB approval is confirmed by issuance of the Form R (“Waiver of Research Participant’s Authorization for Use/Disclosure of PHI for Recruitment”).

Disclosure Tracking Database
Prior to a subject signing the HIPAA Authorization for Research form, any access to patient identifiable data for research purposes must be reported in the Disclosure Tracking Database, even if a Preparatory Research Application or HIPAA Waiver of Authorization has been approved. The database can be accessed at: https://disclose.ucdmc.ucdavis.edu/disclose/index.dsc. Check the box that says “Disclosures for Research (no authorization).” For high volume entries, a spreadsheet may be submitted to HIM for automatic upload. A spreadsheet template with “how-to” instructions is available on the CTSC Clinical Trial Resource Group website (tab “Tools for Study Management”).

At the time of this publication, Health Information Management is planning to launch Quick Disclosure Activity that can be accessed directly in the EMR. With the Quick Disclosure activity, EMR users can quickly and conveniently record what information they release, all from their clinical workspace. For example, after printing patient information from Chart Review and releasing it to their patients, clinicians can use the Quick Disclosure activity to record necessary information about what they released so that it can be included in disclosure reports.

To access the Quick Disclosure
1. Go to Hospital Chart or Chart;
2. Click “More Activities” and choose Quick Disclosure;
3. Quick Disclosure opens. Fill out the appropriate fields.
**Decedent Research**

To look at PHI for decedent research where there are no identifiers linked to living persons and no use of death records, submit a Decedent Research Application. The privacy officer may request proof of death.

If including identifiers linked to living persons or accessing death records maintained by the State Registrar, local registrars, or county recorders, the project must be approved by the IRB in advance.

Upon approval, authorization to access this data will be granted. The application can be found on the Compliance website: [http://www.ucdmc.ucdavis.edu/compliance/guidance/privacy/resdeced.html](http://www.ucdmc.ucdavis.edu/compliance/guidance/privacy/resdeced.html)

**When does HIPAA apply?**

When an established patient is being considered for participation in a research study by a clinician involved in the patient’s care, the HIPAA rules can be confusing. HIPAA applies when a provider is reviewing a patient’s medical record for both treatment and research purposes. In general, under the HIPAA privacy rules, a patient’s medical information may be accessed for a treatment, payment or operational purpose without obtaining prior written consent. Access to a patient’s record for any other purpose may require additional steps to be in compliance with privacy laws and rules. This means that when a provider looks at his or her patient’s medical record for research purposes, the research-related HIPAA rules apply.

**When is access considered to be for a research purpose?**

If a patient’s record is reviewed for a treatment purpose (e.g., to view lab results or consult with a referring provider) the research-related rules do not apply. However, once a patient’s medical information is viewed for a research-related activity (e.g., to screen for eligibility or review, to review a unique case for possible study, or to collect data) the research-related HIPAA rules apply. For example, if a provider is reviewing a patient’s lab report for regular care, this access would be for treatment purposes and the research-related rules would not apply. However, if during this review, the provider notices that the lab value may make them a potential research subject and wants to review the chart further for eligibility, the research-related rules would need to be considered.

**What are the research-related privacy rules that should be considered?**

In general, before any patient information can be used for a research purpose, the patient must sign a study-specific Authorization which recites the patient’s privacy rights. This is true whether or not the patient is seen by the researcher/physician for medical care. Patient information can be used for research-related purposes without a signed patient authorization under two limited exceptions: if the IRS has granted a study a “Form R” or a “Preparatory Research Authorization.” If access to a patient’s medical information is pursuant to one of these exceptions, then any access must be documented and tracking the Disclosure Tracking Database.
IMPORTANT
Any study data obtained without the proper authorizations cited above may
not be used for publication (i.e. journals, abstracts, etc.) or any other purpose
and can be subject to notification requirements under state and/or federal laws.

See Clinical Trials Resource Group’s November 2012 Newsletter for additional
information http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/

8.2 Advertise
The UC Davis IRB must review and approve all materials for human subject
recruitment before recruitment efforts begin. An advertisement to recruit subjects
is any form of materials whose main purpose is to inform and invite the potential
subjects to participate in a research study, including:
• Flyers and handouts
• Bulletin boards/Billboards
• Letters and e-mails
• Newspapers/magazine Ads
• Posters
• Radio, TV and Cable
• Website/Internet postings
• Phone scripts
• Facebook

The advertisement should be limited to the information prospective subjects need to
determine their eligibility and interest, such as:

• Name and address of the investigator or research facility
• The condition under study or purpose of the research
• In summary form, the criteria that will be used to determine eligibility for
  the study
• A brief list of participation benefits, if any
• The time or other commitment required of all subjects
• The location of the research and the phone number of the person or office
to contact for further information

For FDA-regulated research, the advertisement should not:
• Make claims, either explicitly or implicitly, that the drug, biologic or device is
  safe or effective for the purposes under investigation.
• Make claims, either explicitly or implicitly, that the test article is known to be
  equivalent of superior to any other drug, biologic or device.
• Use terms, such as “new treatment,” “new medication” or “new drug” without
  explaining that the test article is investigational.
• Include a coupon good for a discount on the purchase price of the product once it
  has been approved for marketing.
• State or imply a certainty of favorable outcome or other benefits beyond what is
  outlined in the consent document and the protocol.
• Promise “free treatment,” when the intent is only to say subjects will not be
  charged for taking part in the research.
• Include exculpatory language.
• Emphasize the payment or the amount to be paid, by such means as larger or bold type.

8.3 Screen Research Participants

Screening is the term used to describe research activities performed on participants after obtaining their informed consent. Usually screening activities are performed to ensure subjects are eligible to be enrolled in the study, i.e., that the participant meets the inclusion and exclusion criteria for the study. Screening activities include interactions with potential subjects to determine eligibility that would not otherwise have been performed if not for the study. Note that a screen failure is the term used to describe the circumstance in which a subject who has provided consent has subsequently failed to meet eligibility criteria for participation in the study based on screening procedures performed after informed consent was obtained. UC Davis does not have a separate informed consent just for screening. The screening script (i.e. by telephone) has to be approved by the IRB.

8.4 Obtain Informed Consent

Please reference Appendix “Informed Consent”

8.5 Submit a Copy of Consent Form to HIM

Consent Forms for research are required to be in the Legal Medical Record for drug and device studies. Policy & Procedure 2306 (Legal Medical Record Content/Core Elements) requires that the Informed Consent Form must be part of the Legal Medical Record. Under Section VI.E.2.f, (Consents for Care, Treatment and Research/Human Subjects Research involving investigational use of a drug or device), the policy requires that a “signed copy of the consent form is filed in the medical record.” Place these documents in the Health Information Management (HIM) mail baskets located in all patient care areas. Couriers routinely pick these up and all documents are promptly scanned by health information management (HIM) into the medical record. It is important to send the signed ICF’s to HIM as soon as possible since they are held to time standards for scanning documents. The scanned documents can be found under the “Media” tab in the EMR.

The ICF needs to be scanned and uploaded even if the patient does not pass screening criteria.


8.6 Maintain Participant Research Records

Please refer to Activity #11
ACTIVITY #9: Scheduling and Registration

Study subjects have to be flagged in both Invision (Scheduling and Registration System) and EMR. Such flagging achieves the following purposes:

- Separates billing streams to Study Accounts and Insurance Accounts
- Tracks study procedures and services for Health Information Management Disclosures
- Creates flags for billers to issue correct claims

Please note that substantial revisions are in works due to the upcoming release of Epic EMR Research functionality. Please follow CTSC Clinical Trials updates for current information.

9.1 Review Scheduling and Registration Training Materials

- Policy 2382 “Research Subjects Patient Registration, Healthcare Information Collection, Sharing and Maintenance”
- Policy 2317 “Documentation of Research Patient Status in the Electronic Medical Record (EMR)”
- CTSC SOP 10B “Outpatient Scheduling and Registration”
- CTSC SOP 10A “Inpatient, Emergency and Short Stay Research process for registration and Billing”

9.2 Outpatient Studies: Follow CTSC SOP #10B

Refer to the *Coverage Analysis* to determine if there are hospital/clinical charges payable by the study bulk account.
OUTPATIENT Scheduling and Registration: Overview

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-accounts) are used to place study charges that go to the bulk accounts. 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. 47-type accounts will remain open for 999 days, unless explicitly closed by the research team.
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 intrinsically linked with the bulk account number. Where an insurance account has a payer plan code, a 47-account has a bulk account number. In addition, 47-accounts carry embedded hospital code RSH (Research) and plan code 121. 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 (front desk registration staff) can open the 47-accounts.

Three important things to remember about 47-accounts:

1. DO NOT NEED 47-ACCOUNTS for 100% INSURANCE-BILLED STUDIES.
2. 47-ACCOUNT ROUTES CHARGES TO YOUR BULK ACCOUNT
3. NO BULK ACCOUNT = NO 47-ACCOUNT

47-accounts must be created before scheduling an appointment. These accounts are used for outpatient charges only. This path:

- Enables correct routing of charges to bulk accounts
- Enables placing Lab and Rad orders from EMR
- Enables return of Lab and Rad results into EMR
- Used for those procedures in the Coverage Analysis that are labeled “Paid by the Study”

Outpatient Scheduling and Registration: Step-by-Step

1. Create a 47-account for each study subject. Only studies that bill procedures/services to bulk accounts use 47-accounts.

2. Schedule patient visit on a 47-account. If the visit is billed to the bulk account in its entirety, this visit should be scheduled on that patient’s 47-account. However, in many cases the visit would combine procedures billable to insurance and procedures billable to the study. In this case, two scheduling entries must be created, one for routine care (38- or 40-account) and one for research (47-account). This also applies if the PI is treating the patient for routine care issues (unrelated to the trial) during the same visit.

If patient is double-scheduled, the two appointments could be scheduled only 1 minute apart in Invision. Scheduling the same patient on two types of accounts results in two separate encounters in EMR (“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 “office visit” encounter and services billed to the bulk account are placed on the “Research” encounter.

3. Add V70.7 diagnosis code to the problem list. V70.7 plays an important role in tracking research study subjects and the protocol-related orders. The V70.7 diagnosis code is especially important when billing Medicare for research procedures. V70.7 placed in different positions on a claim identifies a patient’s participation in a clinical trial and fulfills the requirements for diagnosis reporting per Medicare rules. This code also helps our own 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. ALL protocol-related services and procedures must be associated with V70.7.

**REMEMBER:** V70.7 diagnosis code does not route the *charges* to insurance/bulk accounts. It routes *information*.

Moreover, all orders associated with V70.7 will be excluded from MyChart. This is critically important for double blinded studies and placebo studies.

Additional information with regard to V70.7 codes can be found in the Clinical Trials Newsletters from January 2013, October 2011, and August 2011 ([http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/](http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/)).

### 9.3 Inpatient, Short Stays, and Emergency: Follow CTSC SOP #10A

Refer to the *Coverage Analysis* to determine if there are hospital/clinical charges payable by the study bulk account.

These types of patients do not have alternative accounts. They are admitted using the usual admission process (10-accounts for inpatient, 50-accounts for short stay, 20-accounts for emergency). 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.”
1. Once the patient is identified as a study patient, you need to modify a Plan Code for each person in the following manner:

<table>
<thead>
<tr>
<th>Inpatient, Emergency and Short Stay</th>
<th>All charges billed to the Sponsor</th>
<th>All charges billed to the Payer</th>
<th>Some charge billed to the Sponsor and some charges billed to the Payer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plan Code (PC)</td>
<td>PC 121 (Research Grants) in primary position</td>
<td>Plan codes as appropriate for the patient’s financial class in the primary and subsequent positions</td>
<td>Plan Code 136 (Research-Needs Review) in the primary position and then other plan codes as appropriate for the patient’s financial class in the subsequent positions.</td>
</tr>
<tr>
<td>Notify MSA unit (CRC/PI Responsibility)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

2. Create the Folder notes, containing contact information of the Principal Investigator (PI), Clinical Research Coordinator (CRC), including name and phone number, the study name and bulk account number (if applicable). To gain access to Folder Notes, submit an on-line Access Request Form. Select “Grant by System” and search for FMS00-C-M (Folder Notes).

In addition, you need to send an e-mail to Medical Services Abstracting (MSA) unit (msaanalystteam@ucdmc.ucdavis.edu) to move the professional charges to bulk accounts as appropriate. The MSA staff will collaborate with the PI/CRC to identify which professional charges should be billed to the patient’s account and which charges should be billed to the bulk account. The charges will be directly posted to the correct account based on this analysis.

### 9.4 Placing Laboratory Orders and Radiology Orders for Research Patients


When placing lab or rad orders, decide whether to place an order on the Office Encounter or Research Encounter. This placement will determine how charges will be routed.
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.

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 the order is billed to the bulk account correctly, 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](http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml).

Microbiology and blinded laboratory orders follow a different path. These orders are placed using specially printed Requisition Forms from Department of Pathology. The paper requisition will need to accompany the specimen to be processed. Please make sure that you have completed the intake process with the Pathology Client Services (916-734-7373) prior to starting the study.

Additional information with regard to placing radiology and laboratory orders is available in the Clinical Trials Newsletter, August 2011 ([http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/](http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/)).
ACTIVITY #10: Investigational Drug Pharmacy

10.1 Review IDS website

According to 21 CFR 312.62(2), an investigator is required to maintain adequate accountability records for the investigational drug or biologic. At UCDHS all investigational drugs or biologics (also known as “test articles”) are handled by the Investigational Drug Services (IDS), a Division of the Pharmacy Department. IDS stores and dispenses drugs in accordance with Good Clinical Practices, the study protocol requirements, and all applicable rules and regulations.

More information about IDS is available here:

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

10.2 Review Investigational Drug Accountability Training

For a thorough training on Investigational Drug Accountability at UCD Medical Center review this material: http://intranet.ucdmc.ucdavis.edu/ctsc/area/cttraining/documents/2012/2012%20Orientation%20Lee.pdf

10.3 Overview of Investigational Drug Management Process at UCDHS

<table>
<thead>
<tr>
<th>IRB Application</th>
<th>Contact IDS</th>
<th>Setup Study</th>
</tr>
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<tbody>
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<td>• Drug preparation</td>
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<td>• Storage</td>
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<tr>
<th>Close Study</th>
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<tr>
<td>• Drug return/destruction</td>
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</tr>
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<td>• Closed out visit</td>
<td>• Drug preparation</td>
<td>• Drug compounding</td>
</tr>
<tr>
<td>• Study archive</td>
<td>• Drug inventory/accountability</td>
<td></td>
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</table>
10.4 **Arrange for Distribution and Maintenance of Investigational Product**

IDS stores and dispenses drugs in accordance with Good Clinical Practices, 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

The 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

The 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.

10.5 **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.

UCDHS Policy and Procedure 1508 “Investigational Drug Distribution” (section III) defines the “administration” of the drug as “the direct application of the drug to the body of the patient or research subject by injection, inhalation, ingestion, or other means.” Specifically, section IV, part H, states that “only physicians, nurses, and authorized licensed personnel will dispense and/or administer investigational drugs and biologics.” In addition, teaching patients to administer (self-administer) a drug or biologic must be done by licensed personnel. Unlicensed personnel (CRCs) may pick up the investigational drug from the IDS in tamper-proof packaging and deliver it to the patient.

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

### 10.6 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.
ACTIVITY #11: Clinical Trial Maintenance

11.1 Reporting New Information

11.1.1 Reporting New information to the IRB

Reference form HRP-213 “Modification” at http://research.ucdavis.edu/f/f#Forms-IRBAAdmin

Reference SOP HRP-024 “New Information” at http://research.ucdavis.edu/gt/d/irb/hrp-024-sop-new-information/view

Please review IRB Training Presentation “Reviewing and Reporting AEs” at http://research.ucdavis.edu/gt/d/irb/reviewing-and-reporting-aes/view

New Information is reported by completing the multipurpose IRB form “Reportable New Information” (HRP-214) http://research.ucdavis.edu/f/f#Forms-IRBAAdmin

This form is used to report a wide spectrum of information to the IRB, including adverse events and protocol deviations. The information that falls into one or more of the following categories needs to be reported to the IRB within 5 business days:

1. **Information that indicates a new or increased risk**, or a new safety issue, for example:
   a. New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) that indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk;
   b. Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm;
   c. Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm;
   d. An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude or a previously known risk, or describe a new risk;
   e. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol;
   f. Changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
2. **Harm experienced by a subject or other individual**, which in the opinion of the investigator are unexpected and probably related (>50% likely; “Don’t know” = <50%) to the research procedures.
   a. A harm is “unexpected” when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population;
   b. A harm is “probably related” to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm.

3. **Non-compliance with the federal regulations** governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.

4. **Failure to follow the protocol** due to the action or inaction of the investigator or research staff.

5. **Change to the protocol** done without prior IRB review to eliminate an apparent immediate hazard to a subject.

6. **Breach of confidentiality**.

7. **Complaint** of a subject that cannot be resolved by the research team.

8. **Premature suspension or termination** by the sponsor, investigator, or institution.

9. **Incarceration of a subject** in a study not approved by the IRB to involve prisoners.

10. **Audit**, inspection, or inquiry by a federal agency or other entity and any resulting reports (e.g., FDA Form 483).

11. **Written reports of study monitors** and data safety reports.

12. **Unanticipated adverse device effect** (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the subjects).

When reporting any of the above, you must also report the date the Investigator became aware of this information, the number of subjects currently enrolled at this organization, whether any currently enrolled subjects are receiving intervention(s) and/or interactions at this organization, and if the study is currently enrolling at this organization. You must also indicate if the protocol and/or the consent document(s) require revision.
11.1.2 Reporting New Information to the FDA

Reporting under IND (Protocol Amendments)
You need to submit an IND Protocol Amendment if you have any of the following changes during the course of your study:

• New Protocol
• Change in Protocol
• New Investigator (new site)

For changes in the Protocol, the IND Protocol Amendment consists of:

• Cover Letter identifying the submission as Protocol Amendment: Change in Protocol or Protocol Amendment: New Protocol (Example)
• Form 1571 - Check an appropriate box under Paragraph 11, “Protocol Amendments”
• A document outlining the differences between the new protocol and the original protocol

The study may begin after you obtain IRB approval based on the new or amended protocol and after the FDA receives the amendment. FDA does not issue “permissions” or “approvals” for protocol amendments, your changes are effective immediately upon the receipt of your amendment by the FDA.

If there are Manufacturing or other changes, such as

• Changes in Chemistry, Manufacturing and Control
• Changes in Pharmacology/toxicology (new findings affecting safety and efficacy)
• Decision to discontinue a clinical study

the company will notify you. Your responsibility is to notify the IRB and make a decision as to whether to proceed with your trial.

Reporting under IDE (IDE Supplements)
Any changes in the Investigational Plan should be approved by the FDA and, when appropriate, IRB, prior to implementing any change to a previously accepted Investigational Plan. The following types of protocol changes would require an approved IDE Supplement, because they are likely to have a significant effect on the scientific soundness of the trial design and/or validity of the data resulting from the trial.

• Change in indication
• Change in type or nature of study control
• Change in primary endpoint
• Change in method of statistical evaluation
• Early termination of the study (except for reasons related to patient safety)
• Change in the number of investigational sites
• Change in the number of study subjects
However, if the modifications meet certain criteria, the sponsor of an IDE may modify the device and/or clinical protocol without prior FDA approval. The sponsor still need to provide notice to FDA within 5 working days of making the change. These notices must be identified as a “notice of IDE change.”

1. **Emergency use.** If the PI deviates from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviations should be reported to the IRB promptly after its occurrence, and to the FDA within 5 working days after the sponsor becomes aware of it.

2. **Certain changes to the device.** Advanced IRB notification is not required if the changes do not constitute a significant change in design or basic operation and are made in response to information gathered during the course of an investigation. Examples include: creditable data generated under the device control procedures (21 CFR Sec. 820.30), preclinical/animal testing, peer reviewed published literature, and clinical information gathered during a clinical trial or marketing.

3. **Certain clinical protocol changes** that do not affect (i) the validity of the data or information resulting from the completion of the approved protocol, or the relationship of the likely patient risk to benefit ratio relied upon to approve the protocol; (ii) the scientific soundness of the investigational plan; or (iii) the rights, safety, or welfare of human subjects involved in the investigation.

4. **If changes will be submitted in the annual report.** A sponsor may make minor changes to an Investigational Plan without prior FDA approval provided that the respective changes are reported in the annual progress report for the IDE (see Annual Reports).


### 11.2 Reporting Adverse Events

#### 11.2.1 Reporting Adverse Events to the IRB

**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 research.
**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 the 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 the risk to the person involved.

Investigators are required to report, with form “Reportable New Information (HRP-214), SAEs as well as other unexpected problems to the IRB within **five business 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/or a multi-site location reported by the sponsor; 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 unexpected; and
4. Is related or probably 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 procedure or if it is more likely than not that the event affects the right and welfare of current participants.

From DHHS Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
This information regarding AEs may impact the risk/benefit ratio. 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 FDA. Such reporting may go through the investigator to the sponsor to the FDA, or in the case of investigator-initiated studies, from Sponsor-Investigator to FDA.

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.

11.2.2 Reporting SAEs to the Sponsor (for Industry or cooperative group studies where the PI is not the Sponsor)

Once an adverse event becomes serious, the site should inform the Sponsor by submitting an SAE report. Typically, the Sponsor will provide the report form to use and inform the study investigator/coordinator where and how (i.e. email, fax, etc) to send the report. An SAE report should be submitted to the Sponsor no later than 24 hours after the site becomes aware of the event. As the site gains more information (i.e. admission records, hospital discharge summaries) updated SAE reports with the new information should be submitted to the Sponsor. In this case the Sponsor (Industry/cooperative group) holds the IND and is therefore responsible for deciding whether the SAE should be reported to the FDA.

11.2.3 Reporting SAEs to the FDA (for investigator-initiated studies under IND or IDE)

IND Safety Reports

**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. 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 initial receipt of the SAE.
In cases where the PI is both the Investigator and the Sponsor, the PI assumes the responsibility of reporting certain SAEs to the FDA. Once it is determined that an SAE must go to the FDA an IND Safety Report is prepared (usually the PI, in association with the medical monitor, will determine whether an IND Safety Report needs to be prepared). An IND Safety Report is an expedited, written notification to the FDA of an adverse experience associated with the use of a study drug that is both serious and unexpected. For filing format and requirements, see http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/step7.html.

For more on filing requirements and follow-up, reference http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/step7.html

IDE Safety Reports
An unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

If the Investigator is a Sponsor-Investigator, he/she will notify the FDA and all participating investigators in a written IDE safety report of any unanticipated adverse device effects. The report is also provided to the device manufacturer and to the reviewing IRB as soon as possible, but no later than 10 working days after the Investigator first learns of the effect. Thereafter the sponsor (or Sponsor-Investigator) shall submit such additional reports concerning the effect as FDA requests.

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046717.htm

11.3 Protocol Deviations
Types of Deviations
A protocol deviation is any departure or discrepancy between the IRB approved protocol and the actual research activities being performed.

Minor protocol deviations are deviations with no substantive effect on the risks to research subjects and that have 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.
Major protocol deviations are deviations that result in or require a substantive action to be taken or result 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.

11.3.1 Reporting Protocol Deviations to the IRB

All protocol deviations from an IRB approved study must be avoided, except to eliminate an immediate hazard to research subjects. Deviations must be reported to the UC Davis IRB in accordance with “Reportable New Information (HRP-214)”, if they fall under the categories listed on the form (see 11.1). Investigators are required to report deviations in these categories to the IRB within 5 working days. Review SOP “New Information (HRP-024)” for how and when to report to the IRB.

11.3.2 Reporting Protocol Deviations to the Sponsor

In many cases Sponsors will specify at the beginning of the study how they would like to handle protocol deviations. Minor deviations (as described above) are usually recorded in the case report forms and tabulated by site at the end of the study. Most Sponsors do not require that minor deviations be reported in any immediate fashion. For major deviations the site often reports to the Sponsor the same information that is reported to the IRB (see major protocol deviations above).

In the case where a site needs a deviation in order to enroll a patient that is not otherwise eligible per the protocol inclusion/exclusion criteria, a Sponsor will request that a planned protocol deviation be filed requesting permission from the Sponsor for the site to enroll the patient. Sponsors will respond to this request in writing and this form along with documentation of all communication between the site and Sponsor should be kept in the patient’s source documentation.

11.3.3 Reporting Protocol Deviations to the FDA (for investigator-initiated studies under IND and IDE)

Reporting Protocol Deviations under IND (adapted from firstclinical.com)

FDA’s regulations have numerous references to “changes” or “amendments” to study protocols. For example, 21 CFR 312.30 addresses the responsibility of sponsors to submit amendments to their IND(s) to ensure that clinical investigations are conducted according to protocols included in the application. 21 CFR 312.30(b) specifically discusses changes in a protocol, and provides several examples of changes that would require sponsors to submit protocol amendments to the IND.
However, the FDA regulations do not provide specific guidance on deviation reporting.

A protocol deviation directed at eliminating an apparent immediate hazard to a research subject or group of subjects may be implemented immediately provided that the reviewing IRB is so notified. The respective protocol deviation should be addressed in the next Annual Report to the IND application. If the protocol deviation will be incorporated as a permanent change (i.e., revision) to the protocol, a respective Protocol Amendment must be submitted prospectively to the IND application/FDA and the revision to the protocol must be approved prospectively by the responsible IRB (see below).

**Reporting Protocol Deviations under IDE**

FDA device regulations at 21 CFR 812.150(a)(4) discuss protocol deviations under IDE regulations. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB should be made aware in accordance with 812.35(a).

**11.4 Reporting Modifications to the IRB (Form HRP-213)**

It is advisable that you consult the UC Davis IRB Investigator Manual (HRP-103) prior to preparing your application. [http://research.ucdavis.edu/c/cs/hrp/documents/HRP103INVESTIGATORMANUAL.docx](http://research.ucdavis.edu/c/cs/hrp/documents/HRP103INVESTIGATORMANUAL.docx)

**Modifications**

Complete the IRB form “Modification” (HRP-213) [http://research.ucdavis.edu/f/f#Forms-IRBAadmin](http://research.ucdavis.edu/f/f#Forms-IRBAadmin)

This form is used to request a modification to previously approved study activity, such as:

- Study Protocol Amendments
- Changes in Research Personnel
- For responses to a Letter of Action (LOA) for requested modifications by the IRB in order to secure approval
Please note that research must continue to be conducted without implementation of the modification until IRB approval is received.

11.5 Submit Continuing Review Progress Reports to the IRB

All studies are required to be reviewed by the IRB at least annually and perhaps more often if the IRB has determined that more frequent review is warranted. Please note that documents reviewed by the IRB are given an expiration date. Using expired consent forms is a common error identified during audits. The IRB sends out a courtesy notice approximately 4 months prior to the approval expiration date, and it is the Principal Investigator’s responsibility to assure that the required updated information is submitted to the IRB by the administrative due date in order to meet the deadline for application to a meeting of the IRB so as to receive approval for the following period prior to the expiration date.

It is advisable that you consult the UC Davis IRB Investigator Manual (HRP-103) prior to preparing your application. (http://research.ucdavis.edu/c/cs/hrp/documents/HRP103INVESTIGATORMANUAL.docx)

The following review 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
- Were 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

- Complete the IRB form “Continuing Review Progress Report” (HRP-212) (http://research.ucdavis.edu/f/f#Forms-IRBAadmin). If the Investigator is requesting any protocol modifications at the time of renewal, complete form HRP-213 Modification Form for submission
- The following documents may be required with your Continuing Review:
  - Clean copies of all consent documents (incorporating any changes being made at this time with new version date) - Clean copies are not required if protocol is permanently closed to enrollment.
If any changes are being made to the consent document(s), submit a *Marked copy indicating changes* being made (with new text underlined or highlighted; language being removed/changed with strike-through; or tracked changes shown – remember to update version date)

If any changes are being made to the *recruitment material(s)*, submit a ‘marked copy’ indicating changes being made (with new text underlined or highlighted; language being removed/changed with strike-through; or tracked changes shown). Also submit a ‘clean copy’ of all recruitment materials/flyers/scripts (incorporating any changes being made at the time with new version date)

Foreign language translated versions of any of the above as applies to your study

Copy of *Sponsor’s progress report(s)* or annual report, if available

Also, if any of the modifications being submitted will include additions or changes to patient care services, a new *Coverage Analysis Qualifying Clinical Trials* (QCT) Form and the billing Grid must be completed

### 11.6 Submit Annual Reports to the FDA

**IND Annual Reports to CDER**

For clinical trials being conducted under an IND, FDA requires an annual report from the Sponsor or Sponsor-Investigator. The annual report is due within 60 days of the anniversary date that the IND went effect (i.e., the date that the FDA permitted the study to begin). Required content is listed in 21 CFR 312.33. For more details, see [http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/step8.html](http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/step8.html).

**IDE Annual Reports to CDRH**

For clinical trials being conducted under an IDE, FDA requires Sponsors to submit progress reports, at regular intervals, and at least yearly. Reports must be submitted to all reviewing IRBs and in the case of significant risk devices the sponsor must also submit the progress report to FDA (21 CFR 812.150). For more details see: [http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/IDE.Step7.html](http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/IDE.Step7.html).

### 11.7 Continue Study Monitoring

See Activity #2.4
11.8 Maintain Study Documentation

“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).

There are many ways to organize essential documents. For example, the ICH GCP E6 guideline recommends that the documents be grouped according to the stage of the trial, i.e. documents relevant to the trial before it commences, documents relevant to the trial during the conduct of the trial, and those documents relevant to the trial after completion or termination of the trial. See http://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial for specific information.

Another way to organize the essential documents into study binders is by the content of the binder. For example, many sites have a “source document binder,” a “case report form binder,” a “financial binder,” and a “regulatory binder.”

The most important thing is that the documentation is organized and that all of the necessary documents are present. This chapter provides examples of a potential system to organize essential documents.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial. These documents are also the ones which are usually audited by the independent audits and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

11.8.1 Regulatory Binder

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.

The following Regulatory Binder Table of Contents is adopted from Partners Healthcare and can be viewed at http://www.partners.org/phsqi/vrb/files/index.htm. The Virtual Regulatory Binder on Partner’s website provides all essential tabs and information about what needs to go under each tab.
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<th>Tab</th>
<th>Documents</th>
<th>Reference to regulations</th>
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<td>Protocol</td>
<td>• Current protocol and all previously approved versions</td>
<td>ICH GCP E6 Sections 8.2.2 &amp; 8.3.2</td>
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<td></td>
<td>• When applicable, a copy of the fully executed protocol signature page for original protocol and all approved versions</td>
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<tr>
<td>CVs &amp; Licensure</td>
<td>• Signed and dated CVs for all study staff</td>
<td>ICH GCP E6 Sections 4.1.1, 8.2.10, 8.3.5</td>
</tr>
<tr>
<td></td>
<td>• Valid medical licenses/professional certifications for all study staff</td>
<td></td>
</tr>
<tr>
<td>Logs</td>
<td>• Pre-Screening Log: Captures subjects who have been pre-screened to determine initial eligibility for enrollment.</td>
<td>ICH GCP E6 Sections 8.3.20, 8.3.25</td>
</tr>
<tr>
<td></td>
<td>• Enrollment Log: Captures all subjects who sign a consent form.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Delegation of Authority/Delegation of Responsibility Log*: Documents the study-related procedures delegated to staff. The PI should initial, sign and date this list, and update it as new staff or study procedures are added to the protocol.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Training Log**: documents training of all study staff on protocol-related procedures.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Adverse Event Tracking Log: Tracks and ensures timely reporting of all applicable adverse events to the IRB. This is often done electronically.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Minor Deviation/Violation Tracking Log: Provides a record of all minor deviations from the approved protocol and facilitates reporting at continuing review. This is often done electronically.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tissues and/or Blood Sample Log: Tracks tissue and/or blood samples collected during research.</td>
<td></td>
</tr>
<tr>
<td>IRB</td>
<td>• Signed and dated submissions:</td>
<td>ICH GCP E6 Sections 8.2.7, 8.2.8, Code of Federal Regulations 45 CRF 46, 21 CRF 50, 21 CRF 56</td>
</tr>
<tr>
<td></td>
<td>• Application</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Continuing Review(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Amendments</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Adverse Events</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Violations/Deviations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Close out Information</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Approval letters and/or notification of IRB decisions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Investigator response(s) to IRB notification (if applicable)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Approved recruitment materials.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Approved educational materials/additional study information distributed to subjects (e.g. subject diary).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Memo regarding FWA, IRB registration. Copy of IRB membership roster.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Any additional correspondence relating to the study (e.g. e-mails).</td>
<td></td>
</tr>
<tr>
<td><strong>Consent/Assent Forms</strong></td>
<td>• Current IRB-approved consent and/or assent form version(s) with the IRB approval stamp.</td>
<td>Code of Federal Regulations 45 CFR 46, 21 CFR 50, 21 CFR 56 ICH GCP E6 Sections 8.2.3, 8.2.7, 8.3.2, 8.3.12</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td><strong>Financial Disclosure</strong></td>
<td>• Signed and dated FDA Financial Disclosures for all clinical investigators listed on the form FDA 1572 (drug) or IRB application (device)</td>
<td>Code of Federal Regulations 21 CFR 54</td>
</tr>
<tr>
<td><strong>Laboratory Documents</strong></td>
<td>• Current Lab Certification (e.g., CLIA, CAP) • Normal Lab/Reference Values</td>
<td>ICH GCP E6 Sections 8.2.11, 8.3.6</td>
</tr>
<tr>
<td><strong>Drug/Device Accountability</strong></td>
<td>• Drug/Device shipment and receipt records • Drug/Device Accountability Log • Most recent version of Investigator’s Brochure or Device Manual</td>
<td>ICH GCP E6 Sections 8.2.14, 8.2.15</td>
</tr>
<tr>
<td><strong>Data Collection</strong></td>
<td>• Blank set of CRFs, data collection sheets, and IRB-approved study questionnaires • If data are being captured electronically a copy of the eCRF completion guidelines could be filed here.</td>
<td>21CFR 312 ICH GCP E6 Sections 8.3.14, 8.3.15, 4.9.3</td>
</tr>
<tr>
<td><strong>DSMB (if applicable)</strong></td>
<td>• Copy of all Data and Safety Monitoring Board (DSMB) reports • Additional correspondences with DSMB (e.g. meeting minutes, information provided to the DSMB, emails)</td>
<td>Guidance for Clinical Trial Sponsors- Establishment and Operation of Clinical Trial Data Monitoring Committees, Section 4.4.3.2</td>
</tr>
<tr>
<td><strong>Correspondence</strong></td>
<td>• All relevant communications, other than site visits, to document any agreement or significant discussions regarding trial or administration, protocol violations, trial conduct, adverse event reporting, etc. • Includes communications to and from the Sponsor and/or the study team • Communications about a specific subject should be filed with source documents for that subject</td>
<td>ICH GCP E6 Sections 8.3.11</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>• Monitoring Log: Documents any form of study oversight/monitoring. Both the monitor and clinical research coordinator should sign the log. • Pre-study Visit Report, Site Initiation Visit Reports, Monitoring Visit Reports, Close-Out visit reports or follow up letters if visit reports are not provided.</td>
<td>ICH GCP E6 Sections 8.2.19, 8.2.20, 8.3.10, 8.4.5</td>
</tr>
<tr>
<td><strong>Subject Identification Code List</strong></td>
<td>• This is a document containing a unique identifier assigned by the investigator to each trial subject to protect the subject’s identity and used in lieu of the subject’s name when the investigator reports adverse events and/or other trial related data.</td>
<td>ICH GCP E6 Sections 1.58, 8.3.21, 8.4.3</td>
</tr>
<tr>
<td><strong>Final Study Report</strong></td>
<td>• Final report by the Investigator to the IRB, and where applicable, to the regulatory authorities to document completion of the trial.</td>
<td>ICH GCP E6 Section 8.4.8</td>
</tr>
</tbody>
</table>
*Delegation of Authority/Responsibilities Log*

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. A Delegation of Authority log should be created documenting delegated tasks to delegated individuals. The same applies to staff/contract organizations not in direct employ of the investigator.

**Example**

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Task(s)</th>
<th>Start Date</th>
<th>End Date</th>
<th>Signature of the delegate</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Smith</td>
<td>CRC</td>
<td>Consent; Delivery of investigational drug from IDS to clinic</td>
<td>1/1/2011</td>
<td>1/31/2012</td>
<td></td>
</tr>
</tbody>
</table>

Signature of the PI  Date

**Training Log**

The investigator has to assure that the staff has appropriate education, training, and experience to perform delegated tasks. The training log should also document that individuals have been trained on protocol-specific topics relevant to their job responsibilities. This training is documented in the training log.

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 a 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, and procedures for ensuring quality control. [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf)

**11.8.2 Source Document Binder**

Per ICH GCP guideline E6 section 5.1 source data is identified 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), and 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 binder:

- 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 Document Binder Table of Content is adopted from Partners Healthcare and can be viewed at http://www.partners.org/phsqi/vrb/files/index.htm.

<table>
<thead>
<tr>
<th>Tab</th>
<th>Documents</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent</td>
<td>Written informed consent form to document that consent is:</td>
<td>OHRP Informed Consent Guidance Information</td>
</tr>
<tr>
<td></td>
<td>Obtained in accordance with regulations, GCP, and protocol</td>
<td>ICH GCP E6 Section 4.8</td>
</tr>
<tr>
<td></td>
<td>Dated prior to participation of each subject in trial.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIPAA form</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subject Bill of Rights</td>
<td></td>
</tr>
<tr>
<td>Records</td>
<td>Includes but not limited to hospital, clinic and office records, progress</td>
<td>ICH GCP E6 Section 1.5.1, 1.5.2, 8.3.13</td>
</tr>
<tr>
<td></td>
<td>notes, medical history, subject diaries, subject questionnaires unless</td>
<td></td>
</tr>
<tr>
<td></td>
<td>accessible via EMR</td>
<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion</td>
<td>Documentation of subject eligibility to be part of the study</td>
<td></td>
</tr>
<tr>
<td>Checklist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correspondence</td>
<td>Notes to file, memos, correspondence, documentation of phone or email</td>
<td></td>
</tr>
<tr>
<td></td>
<td>contact (all subject related)</td>
<td></td>
</tr>
<tr>
<td>Outside reports</td>
<td>Laboratory, x-ray, CT, ECG, etc</td>
<td></td>
</tr>
<tr>
<td>Con Meds, AEs, SAEs</td>
<td>Forms used to collect and document adverse events, concomitant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>medications, serious adverse events, etc.</td>
<td></td>
</tr>
</tbody>
</table>

11.8.3 Case Report Form (CRF) Binder/ Electronic Case Report Form (eCRF)

According to ICH GCP EC 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 (or eCRF) must be supported by source documentation.
At a minimum the CRF should record:

- Inclusion/Exclusion criteria and assessment as to whether the subject met them
- Protocol-specific clinical laboratory testing (including EKGs, X-rays, eye exams, scans, etc) are documented by laboratory records
- All AEs, SAEs, concomitant therapies, and/or inter-current illnesses
- Assessment of severity of AEs, relationship to test article, and expectedness of the AE

One of the most essential tasks performed by the CRC is completing and/or ensuring 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 cannot 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. The correction should be dated and initialed. White-out or eraser 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.

11.8.4 Study Financial Binder

Per CTSC SOPs 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 electronic format).

1. Coverage Analysis (consists of Qualifying Clinical Trial form and Billing Grid) (CTSC SOP#4)

2. For industry-sponsored studies:
   - Internal Budget prepared in the Unified Budget Template (CTSC SOP # 5)
   - External Budget negotiated with the Sponsor (if applicable)
   - Monthly accounts receivable and Invoices to sponsor (CTSC SOP #7)
3. For Grant-or Department-sponsored studies:
   – CTSC budget assessment based on CTSC SOP#6

4. Feasibility assessment - optional (a document outlining the scientific value of the trial and assessing the feasibility of the performance)

5. PFS and PBG bulk account statements and Billing Corrections (CTSC SOP#11)

The following is an outline of the documents that should be kept in the financial binder:

<table>
<thead>
<tr>
<th>Tab</th>
<th>Documents</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coverage Analysis</strong></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 budget. The coverage analysis consists of two parts: Qualifying Clinical Trial Form (QCT) and Billing Grid.</td>
<td>CTSC SOP #4 “Coverage Analysis”</td>
</tr>
<tr>
<td><strong>Internal Budget</strong></td>
<td>• Internal budgets for all clinical trials are based on the coverage analysis and on the contract (if applicable)</td>
<td>CTSC SOP #8 “Completing an internal industry-sponsored clinical trials budget”</td>
</tr>
<tr>
<td><strong>Feasibility Assessment</strong></td>
<td>• This document outlines the scientific importance of the study and balances it with the probability of accrual and financial solvency.</td>
<td>CTSC SOPs #5 (Budget approval for industry-initiated studies”, CTSC SOP #6 “Development of Clinical Trials Budgets for grant proposals”</td>
</tr>
<tr>
<td><strong>Billing Statements</strong></td>
<td>• Monthly billing statements are provided to every coordinator</td>
<td>CTSC SOP#11 “Billing Corrections”</td>
</tr>
<tr>
<td><strong>Signed Agreements with</strong></td>
<td>• This is where agreements between involved parties, if any, are kept. These include Confidential Disclosure Agreements (CDA), Nondisclosure Agreements (NDA), Material Transfer Agreements (MTA), and Clinical Trial Agreements (CTA)</td>
<td>ICH GCP E6 Sections 4.9.6, 5.6, 8.2.6</td>
</tr>
<tr>
<td><strong>external budget</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monthly statements</strong></td>
<td>• Accounting of completed procedures/visits by each patient on the study and rolled-in summary of all patients on the study • Account of Receivables (money owed by a Sponsor based on the completed events)</td>
<td>CTSC SOP#7 “Financial Management of Clinical Trials”</td>
</tr>
<tr>
<td><strong>accounts receivables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invoices to Sponsors</strong></td>
<td>• Invoices generated in Sponsor Format based on the Receivables</td>
<td>CTSC SOP#7 “Financial Management of Clinical Trials”</td>
</tr>
<tr>
<td><strong>and granting agencies</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 11.8.5 IND/IDE Binder (if study is conducted under an IND or IDE)

<table>
<thead>
<tr>
<th>Tab</th>
<th>Documents</th>
<th>Reference</th>
</tr>
</thead>
</table>
| FDA (if study conducted under and IND or IDE) | 1) Clinical Investigator (individual who conducts the study)  
- FDA 1572 (drug) (The form FDA 1572/ Investigator Agreement identifies the facilities where the research will take place, the reviewing/approving IRB and sub-investigators participating in the study. The 1572 should be updated if changes are made during the course of the investigation)  
- Investigator Agreement (device)  
- Serious Adverse Event reports submitted to Sponsor | 21 CFR 312 & 812  
ICH GCP E6  
Section 4.1 |
|     | 2) Sponsor-Investigator (individual who initiates and conducts the study) |                                                 |
|     | - FDA 1572 (drug) (The form FDA 1572/ Investigator Agreement identifies the facilities where the research will take place, the reviewing/approving IRB and sub-investigators participating in the study. The 1572 should be updated if changes are made during the course of the investigation)  
- Investigator Agreement (device)  
- Original application and all subsequent submissions to the FDA:  
  - IND Application (drug)  
  - IDE Application (device)  
  - Amendments to the Application  
  - Adverse Event Reports  
  - Annual Reports  
- Form 3674 (Certification of Registration to ClinicalTrials.gov) | 21 CFR 312 & 812  
ICH GCP E6  
Section 4.1 |

### 11.9 Prepare for Audits

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 deviations and non-compliance and recommend actions.

#### 11.9.1 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, study staff, and investigators. 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** are anticipated upon submission of an IND/IDE application. Selection of study sites may be random or triggered by abnormally high enrollment rate at a given site.

- **For Cause Inspections** – The FDA 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 P&P 1506 [http://intranet.ucdmc.ucdavis.edu/policies/hospital_policies_and_procedures/consents_legal_documents_continued_/1506.shtml](http://intranet.ucdmc.ucdavis.edu/policies/hospital_policies_and_procedures/consents_legal_documents_continued_/1506.shtml).


### 11.9.2 Office of Research Compliance and Integrity

The Office of Research Compliance and Integrity (RCI) fulfills the auditor role for investigator-initiated studies. RCI conducts for-cause reviews (requested by the IRB), random/routine reviews and self-evaluation questionnaires. The purpose of routine/random reviews is to assist investigators with achieving high quality of regulatory compliance. The reviews are meant to be more educational rather than punitive in nature. RCI summarizes and reports the findings directly to the investigators. The reviewer expects the investigators to provide the notification of findings or modifications to the IRB; then the reviewer monitors the IRB records for completion.

### 11.9.3 CTSC Clinical Trials Group – SMART Monitoring and QA program

For concerns about preparedness for an audit, contact the Clinical Trials Resource Group. We offer audit readiness assessment for both industry and investigator-initiated studies. This program helps ensure compliance with FDA, GCP, and IRB regulations, and UC Davis Health System SOPs and P&Ps as related to clinical research. The results of the pre-audit assessment will be provided for investigators and teams. For further information see [http://www.ucdmc.ucdavis.edu/clinicaltrials/monitoring/index.html](http://www.ucdmc.ucdavis.edu/clinicaltrials/monitoring/index.html)
ACTIVITY #12: Billing and Invoicing

12.1 Verify Bulk Account Statements, Resolve Issues with Patient Financial Services

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 incorrect charges are identified, refer to CTSC SOP#11 “Research Billing Corrections” for detailed information on how to correct the charges.

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

12.2 Maintain Log of Completed Study Procedures for Billing/Invoicing Reference

The Study Coordinator (CRC) updates enrollment log and individual schedule of events for each study week, and reviews the actual and projected recruitment with the clinical research manager. The information on the schedule of events shows actual visit dates and has a notation what services and procedures were completed during that visit.

An example of visit tracking is shown here:

![Visit Tracking Example](image)

A financial analyst uses this information to convert completed visits into Receivables by using the contracted amounts per visit/procedure. All costs for rescheduled visits, delayed procedures, adverse events and any other “invoiceable” items are also captured at this time. Costs for procedures fluctuate at various times throughout the year. Check charges on your bulk accounts to make sure the charges correspond to what you budgeted.
An example of Receivables tracking is shown here:

For details see CTSC SOP#7 “Financial Management of Clinical Trials”

### 12.3 Prepare Invoices for the Sponsor

The resulting summary of occurred costs is transferred on the Invoice sent to the Sponsor. The invoice is prepared and formatted in accordance with payment terms outlined in the contract and is sent to the sponsor.

In addition, the CRC, the clinical research manager and the financial analyst analyze the projected visit schedule based on likely dates of future patient/last visit. This data support estimates of the projected study revenue. The logs and invoices are stored in the Financial Binder.

Hospital Policies and Procedures P&P 1802 and P&P 1816 require that all departments prepare a DaFIS Accounts Receivable entry to reflect amounts due to the University from the study sponsors for services rendered. Since each clinical trial contract has unique terms and payment schedules, a separate accounts receivable file for each contract should be established to house data for invoice preparation. The same amount as on the sponsor invoice is entered into the DaFIS system Research payments (cash collection) should be directed to the CRC’ departmental address. Once received, the cash payment is reconciled against outstanding invoices and DaFIS AR entries. 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 can request a detailed breakdown of the payment from the sponsor.

12.4 PI Minimum Effort recovery for PRDRUG trials

A PI must dedicate a minimum of 1% effort to a clinical trial in PRDRUG fund category (industry-sponsored clinical trial). This effort can either be cost shared or directly charged to the trial (CTSC SOP#7 and CTSC SOP#9). “Cost shared” means committed time that is paid by sources other than the extramurally funded project; “direct charged” means committed time that is paid (i.e., directly charged) by the extramurally funded project. At the end of the trial, a review must be completed to ensure full project costing before a residual balance may be transferred to a R & E account:

a. The principal investigator minimum effort of 1% must be charged for the length of the trial. If it was previously cost shared, this cost sharing must be replaced with charged effort.

  For example:
  For a five year trial for a PI earning $100,000 per year in X + Y salary, $5,000 must be charged to the trial account. For non-federal projects, this transaction may be posted to recent pay periods for ease of administration.

b. If the actual effort, calculated by the number of hours spent on the project from the UBT exceeds the minimum 1% estimate, the actual effort should be charged.

  For example:
  Per UBT, the following PI effort hours are stated:
  30.5 hrs in start up
  2 hrs in close out
  13 in invoiceables
  18.5 per patient (10 patients), total of 185 hrs
  Total 230.5 hrs

  For a PI earning $100,000 per year, the hourly rate is $47.90 per hour ($100,000 / 2088 hrs). The actual charge to the project should be $11,000 prior to any transfer of residual funds. For non-federal projects, this transaction may be posted to recent pay periods for ease of administration.
ACTIVITY #13: Study Closure

13.1 Close Bulk & DaFIS Accounts

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 (Kuali) account.

13.2 Notify IRB About Permanent Study Closure

Complete the FORM “Continuing Review Progress Report (HRP-212),” attach all requested supplements, have the formed signed by the individuals listed in the form, and provide the requested number of copies to the IRB Administration. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Reference the Investigators Manual (HRP-103) for further information http://research.ucdavis.edu/c/cs/hrp/documents/HRP103INVESTIGATORMANUAL.docx

13.3 Notify Investigational Drug Services (IDS) for Study Drug Disposal

Once all study drugs and devices have been accounted for, the coordinator must work with IDS staff to close the study at the pharmacy.

13.4 Notify Health System Contracts

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. http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/contactus.html

13.5 Archive Documents

For drugs, according to 21 CRF 312.62(c), an investigator shall retain records required to be maintained under the 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 applications is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

For devices, according to 21 CRF 812.140(d), an investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.
APPENDIX 1: Informed Consent

Most of the questions about Informed Consent can be answered by:

UC Davis IRB SOP HRP-090 Informed Consent Process for Research.

UC Davis IRB SOP HRP-091 Written Documentation of 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. 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. Rather than an endpoint, the consent document should be the basis for a meaningful exchange between the investigator and the subject.

- 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.

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 UC Davis (UCD) SOP HRP-013 to determine which individuals may serve as legally authorized representatives.
Informed Consent is required if the study involves:

- living individuals about whom an investigator conducting the research obtains (1) data through intervention or interaction with the individual, or (2) information is both private information and identifiable information
- a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge
- use of human organs, tissue, or biological fluids
- clinical data or other sensitive personal information
- investigational drugs and devices
- surveys/questionnaires
- research meets the State of California’s definition of a “medical experiment”

Informed Consent is not required if the study involves:

- Observation of legal public behavior
  - unless interaction with the subjects occur
- Study of existing publicly available data/records
  - unless interaction with the subjects occur
- Normal educational practices
  - unless interaction with the subjects occur
- 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

Waiver or Alteration of Informed Consent may be given if:

- The research is not FDA regulated
- The research does not involved non-viable neonates
- The research does not meet the State of California’s definition of a “medical experiment”
- 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

* For a list of all criteria for an alteration or waiver of informed consent to be given at UCD see HRP-410 Waiver or Alteration of the Consent Process.

Subjects should be consented prior to:

- Screening procedures performed solely for eligibility determination
- Altering the subject’s care for the purpose 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), each of the six elements of 21 CFR 50.25(b) that is appropriate to the study, and the element in 50.25(c) for clinical trials posted on clinicaltrials.gov. IRBs have the final authority for ensuring the adequacy of the information in the informed consent document.

21CFR 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 21CFR 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.

**Elements of Informed Consent (FDA Regulations 21 CFR 50.25)**

(a) Basic elements of informed consent.

(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.

If a conflict of interest has been determined by the Research Compliance and Integrity (RCI) unit, then this conflict must be disclosed within the consent form to the participants. University of California Office of the President (UCOP) has approved the following language for UCD, “This research is being funded by [Insert name of sponsor. If any personal or institutional conflicts have been identified, add additional language consistent with RPAC Op. Guid. 11-04: http://www.ucop.edu/raohome/cgmemos/11-04.pdf].
(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 description of the important risks/benefits of the alternatives should be included 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 might inspect study 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.

UCOP has approved the following language for UCD, “Efforts will be made to limit use or disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the IRB and other University of California representatives responsible for the management or oversight of this study. The sponsor, monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your research records to conduct and oversee the study. We may publish the results of this research. However, we will keep your name and other identifying information confidential.”
(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.

UCD IRB provides the following UCOP approved wording “If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your insurance company just like other medical costs.”

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. Preferred UCOP approved wording is: “The University and the study sponsor do not normally provide any other form of compensation for injury.” 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.

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 legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence., see 21 CFR 50.20.

(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 research personnel 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. In addition, a 24-hour emergency number should also be included within the consent form for emergency situations outside of regular business hours. The IRB also requires that the IRB contact information be provided within the consent form to answer any research related questions.
(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.

Preferred UCOP approved wording, “You may decide not to take part in the research and it will not be held against you.”

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 (provided when appropriate)

(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.

Preferred UCOP approved wording, “The procedures in this research are known to hurt a pregnancy or fetus in the following ways: [Omit the previous sentence if there are no known risks.] The research may also hurt a pregnancy or fetus in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death. [Omit the previous two sentences for research whose risk profile in pregnancy is well known.] You should not be or become pregnant [include as applicable “or father a baby”] while on this research study.”
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.

For FDA regulated research, subjects that wish to withdraw from the study must be informed that already collected data from research cannot be removed from the research database.
(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.

**Appropriate Use of Language**

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**

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.

- 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 has to approve the changes to the informed consent document prior to utilization by research personnel. In addition, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version. Recommendation from most IRB’s is that the investigator places version dates within the informed consent document. 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](http://research.ucdavis.edu/gt/g)
- Use short sentences < 15 words
- Use active form
- 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 approves the translated ICF.

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 and the IRB has approved the research for inclusion of non-English speaking subjects, 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. The UC Davis IRB has a list of pre-approved short forms available for this use. 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. An impartial 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 and a copy of the summary. The witness must sign and date both the short form and a copy of the summary, and the person actually obtaining the consent must sign and date the short form and a copy of the summary. The subject or the representative must be given a copy of the signed and dated summary as well as a copy of the signed and dated short form.

For specific guidance on using “short forms” at UC Davis see HRP-090 Informed Consent Process for Research.

**Illiterate 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. In addition, if a subject is unable to read or if a legally authorized representative is unable to read, an impartial witness must be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject’s legally authorized representative, and after the subject or the subject’s legally authorized representative has orally consented to the subject’s participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject’s legally authorized representative, and that informed consent was freely given by the subject or the subject’s legally authorized representative.

For specific guidance on using “short forms” at UC Davis see HRP-090 Informed Consent Process for Research and HRP-091 Written Documentation of Consent.
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 subjects 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.

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

Unless the IRB has waived the requirement to obtain consent, when research involves children consent may only be obtained from biologic or adoptive parents or an individual legally authorized to consent on behalf of the child to general medical care. Before obtaining permission from an individual who is not a parent, contact legal counsel (HRP-013 Legally Authorized Representatives, Children, and Guardians').
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, if applicable, 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).

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 presents 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

Please see Activity # 4.1.6 for more detailed explanation of Subject Injury.

**Documentation of Informed Consent**

A signed and dated consent form is not sufficient in documenting the informed consent process for clinical trials. 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 (see SOP HRP-091 Written Documentation of Consent).

In limited circumstances, the IRB can waive the requirement for the investigator to obtain a written documented (signed) consent form for some or all research participants (HRP-411).

**A. Risk of Breach of Confidentiality**

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.
• The research does not meet the State of California’s definition of a medical experiment

**B. Minimal Risk Research**

The IRB can waive the requirement for written documentation of informed consent for non-exempt research if all 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.
• The research does not meet the State of California’s definition of a medical experiment.
• Written information describing the research is to be provided to the subject or the subject’s legally authorized representative,

-OR-

• Written information describing the research does not need to be provided to the subject or the subject’s legally authorized representative

**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, online, or presented orally). This information must include the 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 document 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.

**Waiver or Alteration of the Consent Process (HRP-410)**

If the study falls under the State of California Definition of a medical experiment, the waiver cannot be granted.

A “medical experiment” is defined in the California Health and Safety Code Section 24174, as

(a) The severance or penetration or damaging of tissues of a human subject or the use of a drug or device, as defined in Section 109920 or 109925, electromagnetic radiation, heat or cold, or a biological substance or organism, in or upon a human
subject in the practice or research of medicine in a manner not reasonably related
to maintaining or improving the health of the subject or otherwise directly
benefiting the subject.

(b) The investigational use of a drug or device as provided in Sections 111590 and
111595.

(c) Withholding medical treatment from a human subject for any purpose other than
maintenance or improvement of the health of the subject.

If it does not fall under this definition then other criteria must be met in order to
justify the Waver of Informed Consent process (see HRP-410 for options).

Separate provisions are given for FDA-regulated research involving anonymous
tissue specimens (in vitro diagnostic studies with leftover human specimens that are
not individually identifiable) and Planned Emergency Research.

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. This is considered to be an alteration of the informed consent process
and must meet specific Federal and State regulations for approval.
Consenting Patients for Data Use in Advertising and Social Media


The actual consent form can be found on the Patient Care Services website under the heading PCS Templates: [http://intranet.ucdmc.ucdavis.edu/pcs/templates/AuthorizationforTraining.pdf](http://intranet.ucdmc.ucdavis.edu/pcs/templates/AuthorizationforTraining.pdf)

California Subject Bill or Rights

California Assembly Bill 1752 and the Health and Safety Code’s definition of medical experimentation encompasses almost all studies involving biomedical procedures, placebo controls, innovative therapy, and/or normal volunteer subjects. Thus, for these types of studies, the Experimental Subject’s Bill of Rights must be given to subjects along with a copy of the consent form or information sheet for the study. There should be a reference at the end of the consent form indicating that the subject has received or will receive the Experimental Subject’s Bill of Rights.

Experimental Subject’s Bill of Rights

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study.
  - The procedures to be followed.
  - Any drug or device to be used. [Delete if there are no drugs and devices used.]
  - Any common or important discomforts and risks.
  - Any benefits you might expect.
  - Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study. [Delete for research involving no alternatives.]
  - Medical treatment, if any, that is available for complications. [Delete for research involving no more than minimal risk.]
- Whether or not you take part is up to you.
- You can choose without force, fraud, deceive, duress, coercion, or undue influence.
- You can choose not to take part.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to take part, you will be given a signed and dated copy of this document. [Delete if the consent process will not include obtaining signatures on the consent document.]
- If you agree to take part, you will be given a copy of this document. [Delete if the consent process includes obtaining signatures on the consent document.]
## APPENDIX 2: Comparison of Abbreviated and Full IDE Requirements

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<th>Item</th>
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<td>Select qualified investigators</td>
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<td>Provide investigators with needed information to conduct study</td>
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<td><strong>Selecting Investigators and Monitors</strong></td>
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<td>Ship device only to investigators</td>
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## Supplemental Checklist for Investigators and Staff

### Helpful Contacts

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<tr>
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<tbody>
<tr>
<td>Kate Marusina</td>
<td>Manager Clinical Trials, CTSC</td>
</tr>
<tr>
<td>Suzan Bruce</td>
<td>PRAIV, Clinical Trials, CTSC. Clinical Research Billing Lead</td>
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<tr>
<td>Tracy Hysong</td>
<td>Regulatory Analyst, Clinical Trials, CTSC. FDA and Monitoring Lead</td>
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<tr>
<td>Virina De Jesus</td>
<td>Sr. Clinical Research Coordinator, Clinical Trials, CTSC. CRC mentoring and Coordinator-for-Hire Lead</td>
</tr>
<tr>
<td>Elizabeth Mathis</td>
<td>Clinical Research Coordinator, Clinical Trials, CTSC. Educational Program Lead</td>
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<tr>
<td>Daniel Popescu</td>
<td>Office of Research Compliance and Integrity</td>
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<tr>
<td>Helen del Rio</td>
<td>Health System Compliance Billing Analyst</td>
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<td>Athina Addison</td>
<td>Patient Financial Services</td>
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<tr>
<td>Sadia Ramay</td>
<td>Professional Billing Services</td>
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<tr>
<td>Miles McFann</td>
<td>Outreach and Training Education Analyst</td>
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<td>Julie Calahan</td>
<td>Budget Analyst, Health System Contracts – Clinical Trials Contracts</td>
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<td>Erick Jenkins</td>
<td>Manager, health System Contracts - Clinical Trials Contracts</td>
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<td>Nicole Hansen</td>
<td>CTSC Clinical Research Center</td>
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<td>All clinical trials related</td>
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<td>Coverage Analysis, coding for research procedures</td>
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<td>Preparation of internal study budgets</td>
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<td>Negotiation of clinical trials contracts with industry sponsors</td>
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<td>Conducts your clinical study in a stand-alone research center</td>
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## Activity #1. Complete Necessary Training

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<thead>
<tr>
<th>UCD Research Guidebook Page Number</th>
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</table>
| Become aware of laws governing Clinical Research | FDA: [www.fda.gov](http://www.fda.gov)  
NIH: [www.nih.gov](http://www.nih.gov)  
Code of Federal Regulations:  
21CFR312 (drugs, biologics);  
21CFR812 (devices);  
45CFR46 (the common rule);  
[http://ecfr.gpoaccess.gov](http://ecfr.gpoaccess.gov) |
<p>| Read Clinical Trials SOPs housed by CTSC | <a href="http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml">http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml</a> |
| CITI training | <a href="http://research.ucdavis.edu/c/cs/hrp/roe">http://research.ucdavis.edu/c/cs/hrp/roe</a> |
| Dangerous Goods Shipping, Infectious Substances &amp; Dry Ice | <a href="http://lms.ucdavis.edu">http://lms.ucdavis.edu</a> |</p>
<table>
<thead>
<tr>
<th>Social and Behavioral studies</th>
<th>Therapeutic Interventional Studies (FDA regulated)</th>
<th>Non-Interventional Studies (including chart reviews, outcome databases, retrospective analysis)</th>
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### Activity #2. Study development and feasibility

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<th>Links</th>
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<tbody>
<tr>
<td>Contact CTSC for support with study start-up and maintenance</td>
<td><a href="http://www.ucdmc.ucdavis.edu/clinicaltrials/Forinvestigators/index.html">http://www.ucdmc.ucdavis.edu/clinicaltrials/Forinvestigators/index.html</a></td>
</tr>
<tr>
<td>Request access to PHI data for preparatory research (if applicable)</td>
<td><a href="http://www.ucdmc.ucdavis.edu/compliance/guidance/privacy/resprep.html">http://www.ucdmc.ucdavis.edu/compliance/guidance/privacy/resprep.html</a></td>
</tr>
<tr>
<td>Create Monitoring Plan (if applicable)</td>
<td><a href="http://www.ucdmc.ucdavis.edu/clinicaltrials/Monitoring/index.html">http://www.ucdmc.ucdavis.edu/clinicaltrials/Monitoring/index.html</a></td>
</tr>
<tr>
<td>Create DSMB/C (if applicable)</td>
<td><a href="http://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf">http://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf</a></td>
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<tr>
<td>Social and Behavioral studies</td>
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Activity #3. IND/IDE Submissions (this page applies ONLY to Therapeutic Interventional Studies (FDA regulated))

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<th>UCD Research Guidebook Page Number</th>
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**IND (investigational drugs, biologics, dietary supplements)**

- Learn about regulatory requirements for clinical studies involving a drug, biologic, or dietary supplement
- Good Laboratory Practices
- Learn about INDs, IND subtypes, and NDAs
- Determine if your study is exempt from IND requirements

**IDE (investigational devices)**

- Learn about regulatory requirements for clinical studies involving a device
- Good Laboratory Practices
- Learn about Device Classification and Significant Risk (SR) vs. not Significant Risk (NSR)
- Learn about IDEs, IDE subtypes, 510(k), and PMA
- Determine if your study is exempt from IDE requirements

**BOTH IND and IDE**

- Learn about Sponsors, Investigators, and Sponsor-Investigators
- Learn about Sponsor-Investigator responsibilities under IND/IDE
- Contact CTSC Clinical Trials for assistance with IND or IDE
<table>
<thead>
<tr>
<th>Links</th>
<th>Therapeutic Interven-tional Studies (FDA regulated)</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="http://fda.yorkcast.com/webcast/Viewer/?peid=8553ad7df9054febb5ef0048e359ad1e1d">http://fda.yorkcast.com/webcast/Viewer/?peid=8553ad7df9054febb5ef0048e359ad1e1d</a></td>
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<tr>
<td><a href="http://www.fda.gov/Training/CDRHLearn/ucm162015.htm#overview">http://www.fda.gov/Training/CDRHLearn/ucm162015.htm#overview</a></td>
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</table>
## Activity #4. Prepare documentation

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<th>Activity</th>
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<tr>
<td><strong>Financial Approval</strong></td>
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<tr>
<td>Review CTSC SOPs 5, 6, 7, 8, 9</td>
<td></td>
<td><a href="http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml">http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml</a></td>
</tr>
<tr>
<td>Learn about subject injury</td>
<td></td>
<td><a href="mailto:risk.management@ucdmc.ucdavis.edu">risk.management@ucdmc.ucdavis.edu</a> or (916) 734-3883</td>
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<td>Prepare budgets for Investigator-Initiated studies</td>
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<tr>
<td><strong>Regulatory Approval</strong></td>
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| Obtain additional approvals as necessary (radiology, stem cell, recombinant DNA, etc) | | Radiology: [http://intranet.ucdmc.ucdavis.edu/safety/hp/](http://intranet.ucdmc.ucdavis.edu/safety/hp/)  
<p>| Learn about compensation for participation in research | | <a href="http://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm">http://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm</a> |
| <strong>Administrative Approvals Form</strong> | | |
| PI and Department Chair must sign HRP-226 (Administrative Approvals Form). | | <a href="http://research.ucdavis.edu/f/f#Forms-IRBAdmin">http://research.ucdavis.edu/f/f#Forms-IRBAdmin</a> |</p>
<table>
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<tr>
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</table>
### Activity #5. Submit to IRB and Obtain IRB Approval

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<tr>
<th>Activity</th>
<th>UCD Research Guidebook Page Number</th>
<th>Links</th>
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</table>
| Submit required documents to IRB | | eDocs: [http://research.ucdavis.edu/edocs](http://research.ucdavis.edu/edocs)  
| Respond to IRB comments and obtain IRB approval | | |

### Activity #6. Obtain Approval by HS Contracts


<table>
<thead>
<tr>
<th>Activity</th>
<th>UCD Research Guidebook Page Number</th>
<th>Links</th>
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<tbody>
<tr>
<td>Contract negotiation and execution (for industry funded studies only)</td>
<td></td>
<td><a href="http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/">http://www.ucdmc.ucdavis.edu/healthsystemcontracts/clinicaltrialscontracts/</a></td>
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Contract negotiation and execution (for industry funded studies only) [link]

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**SUPPLEMENTAL CHECKLIST**
Activity #7. Study Activation

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<tr>
<th>Activity</th>
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<tbody>
<tr>
<td>Open DaFIS account</td>
<td></td>
<td><a href="http://dafis.ucdavis.edu/index.cfm">http://dafis.ucdavis.edu/index.cfm</a></td>
</tr>
<tr>
<td>Open Bulk Account (if needed)</td>
<td></td>
<td>[<a href="http://intranet.ucdmc.ucdavis.edu/researchbudgeting/b">http://intranet.ucdmc.ucdavis.edu/researchbudgeting/b</a> budgeting/index.shtml](<a href="http://intranet.ucdmc.ucdavis.edu/researchbudgeting/b">http://intranet.ucdmc.ucdavis.edu/researchbudgeting/b</a> budgeting/index.shtml)</td>
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Activity #8. Subject Recruitment

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<tr>
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<tbody>
<tr>
<td>Screen research participants</td>
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<tr>
<td>Submit copy of consent to HIM (Health Information Management)</td>
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<td>Policy &amp; Procedure 2306 <a href="http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml">http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml</a></td>
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### Activity #9. Scheduling and Registration

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#### OUTPATIENT STUDIES

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#### IN-PATIENT, SHORT-STAYS, and EMERGENCY

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### Activity #10. Investigational Drug Pharmacy

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### Activity #11. Clinical Trial Maintenance

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<tr>
<td>Reporting to the IRB</td>
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<td>Reporting New Information</td>
<td>[<a href="http://research.ucdavis.edu/f/f#Forms-IRBAdmin">http://research.ucdavis.edu/f/f#Forms-IRBAdmin</a> (HRP-214)]</td>
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<tr>
<td>Reporting Adverse Events</td>
<td>[<a href="http://research.ucdavis.edu/f/f#Forms-IRBAdmin">http://research.ucdavis.edu/f/f#Forms-IRBAdmin</a> (HRP-214)]</td>
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<tr>
<td>Reporting Protocol Deviations</td>
<td>[<a href="http://research.ucdavis.edu/f/f#Forms-IRBAdmin">http://research.ucdavis.edu/f/f#Forms-IRBAdmin</a> (HRP-214)]</td>
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<tr>
<td>Reporting Protocol Modifications</td>
<td>[<a href="http://research.ucdavis.edu/f/f#Forms-IRBAdmin">http://research.ucdavis.edu/f/f#Forms-IRBAdmin</a> (HRP-213)]</td>
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<td>Submit Continuing Progress Reports</td>
<td>[<a href="http://research.ucdavis.edu/f/f#Forms-IRBAdmin">http://research.ucdavis.edu/f/f#Forms-IRBAdmin</a> (HRP-212)]</td>
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<td>Maintain Study Documentation</td>
<td>[<a href="http://www.partners.org/phsqi/vrb/files/index.htm">http://www.partners.org/phsqi/vrb/files/index.htm</a>]</td>
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**Continue with Study Monitoring**


**Prepare for Federal and Sponsor Audits**

FDAs Bioresearch Monitoring Program [http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm160670.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm160670.htm)

**Reporting to FDA and Sponsors**

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<td>Mandatory if Investigator is IND or IDE holder</td>
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### Activity #11. Clinical Trial Maintenance (continued)

<table>
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<tr>
<th>UCD Research Guidebook Page Number</th>
<th>Links</th>
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</table>
| **Submit Annual Reports to CDER or CDRH** | IND: [http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/step8.html](http://www.ucdmc.ucdavis.edu/clinicaltrials/IND/step8.html)  
| **Maintain Study documentation** | [http://www.partners.org/phsqi/vrb/files/index.htm](http://www.partners.org/phsqi/vrb/files/index.htm) |
| **Prepare for Federal and Sponsor Audits** | FDAs Bioresearch Monitoring Program: [http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm160670.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm160670.htm)  
P&P 1506 |

### Activity #12. Billing and Invoicing

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<tr>
<td><strong>Verify bulk account statements, resolve issues with Patient Financial Services</strong></td>
<td>CTSC SOP#11 <a href="http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml">http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml</a></td>
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<tr>
<td><strong>Maintain log of completed study procedures for billing/invoicing reference</strong></td>
<td>CTSC SOP #7 <a href="http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml">http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml</a></td>
</tr>
<tr>
<td><strong>Prepare invoice for the Sponsor</strong></td>
<td>CTSC SOP #7 <a href="http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml">http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml</a></td>
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<td><strong>PI minimum effort recovery in PRDrug subfund trials</strong></td>
<td>CTSC SOP #9 <a href="http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml">http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml</a></td>
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**Social and Behavioral studies**

- **Therapeutic Interventional Studies (FDA regulated)**
  - Mandatory
  - Mandatory
  - Mandatory
  - Mandatory

- **Non-interventional studies (including chart reviews, outcome databases, retrospective analysis)**
  - Not Applicable
  - Mandatory
  - Not Applicable
  - Not Applicable

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**Mandatory Effort in PR Drug Subfund Trials**

- CTSC SOP #9
- http://intranet.ucdmc.ucdavis.edu/ctsc/area/clinicaltrials/processmaps.shtml

- Not applicable
- Mandatory
- Not Applicable
- Not Applicable
## Activity #13. Study Closure

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