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](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).
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 Laffoday (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](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.

### 2.7 Contact Investigational Drug Services

See Activity 10 for detailed description of the Investigational Drug Services (IDS), start-up requirements and fees.