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](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](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](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