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/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>
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<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>
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</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.

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/).

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.
Budget tips:

“Don’t miss Hidden Costs-create correct budgets for Industry-Sponsored studies” (Clinical Trials Newsletter v 9, June 2012);
“Find the break-even point for clinical trial budgets using a new tool” (Clinical Trials Newsletter v 7, November 2011);

http://intranet.ucdmc.ucdavis.edu/ctsc/area/ctnewsletters/

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/c clinicaltrials/processmaps.shtml](http://intranet.ucdmc.ucdavis.edu/ctsc/area/c 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-IRBAdmin) 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 the 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


**HRP Form 211-Application for Initial Review**

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:

**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-IRBAadmin](http://research.ucdavis.edu/f/f#Forms-IRBAadmin))
  – 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 preparatory 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_i/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