

**RM 200**  
**STANDARD OPERATING PROCEDURES FOR**  
**REGULATORY MANAGEMENT**

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## RM 201 CLINICAL TRIAL REGULATORY OVERVIEW

### 1. PURPOSE

The purpose of this document is to provide an overview of the process for initiating clinical drug and device studies.

### 2. PROCEDURE

#### A. Preliminary Assessment

Proposed clinical research studies are either presented internally (investigator initiated) or externally (from an outside sponsor). Upon receiving an externally generated study, the Principal Investigator (PI) must review the study to determine if he/she has any interest in the proposed research. If the PI is interested in the study a study coordinator will be assigned and the study will follow the regulatory submission process as outlined below. If the PI has no interest in the study the study sponsor will be notified and no further action will be taken.

#### B. CRC/Regulatory Coordinator Assignment

If the department has adequate staffing and facilities to conduct the study, a CRC and/or Regulatory Coordinator will be assigned to the protocol. It is the responsibility of the CRC or Regulatory Coordinator to prepare and to submit the required documents for approval. For most cooperative group studies, a regulatory coordinator will prepare the Human Subjects packet and the assigned CRC will review it for accuracy before IRB submission. These documents include IRB forms, consent forms, and regulatory documents.

#### C. Regulatory Documents

Each new industry and some investigator-initiated studies require documentation to be submitted to the sponsor showing eligibility, standards, and participation of the institution and investigator. Listed below are the standard required forms and documents that should be submitted to the sponsor prior to patient enrollment.

- i. **Form FDA 1572** (available on the FDA website): This form is required by the Department of Health and Human Services (DHHS). No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator Form FDA 1572. A signed and dated Curriculum Vitae (CV) for the investigator listed must be included with the FDA Form 1572.
- ii. **Additional CVs** (One signed and dated CV must be included for each co-investigator listed on FDA Form 1572.
- iii. **Medical Licensure**: One current medical license must be included for each investigator or co-investigator listed on FDA Form 1572.
- iv. **Laboratory Certification**: Laboratories utilized on the study must be listed on the FDA Form 1572. A Clinical Laboratory Institutional Accreditation (CLIA) Laboratory Certificate of Accreditation must be included along with the lab license.

- v. **Laboratory Normals:** Current lab normal values for each test required by the study must be included. If there is more than one lab facility listed on the 1572, lab values must be included for each laboratory facility.
- vi. **IRB Member List** (available through the IRB Administration): Member lists from both IRB committees (A and B) must be included

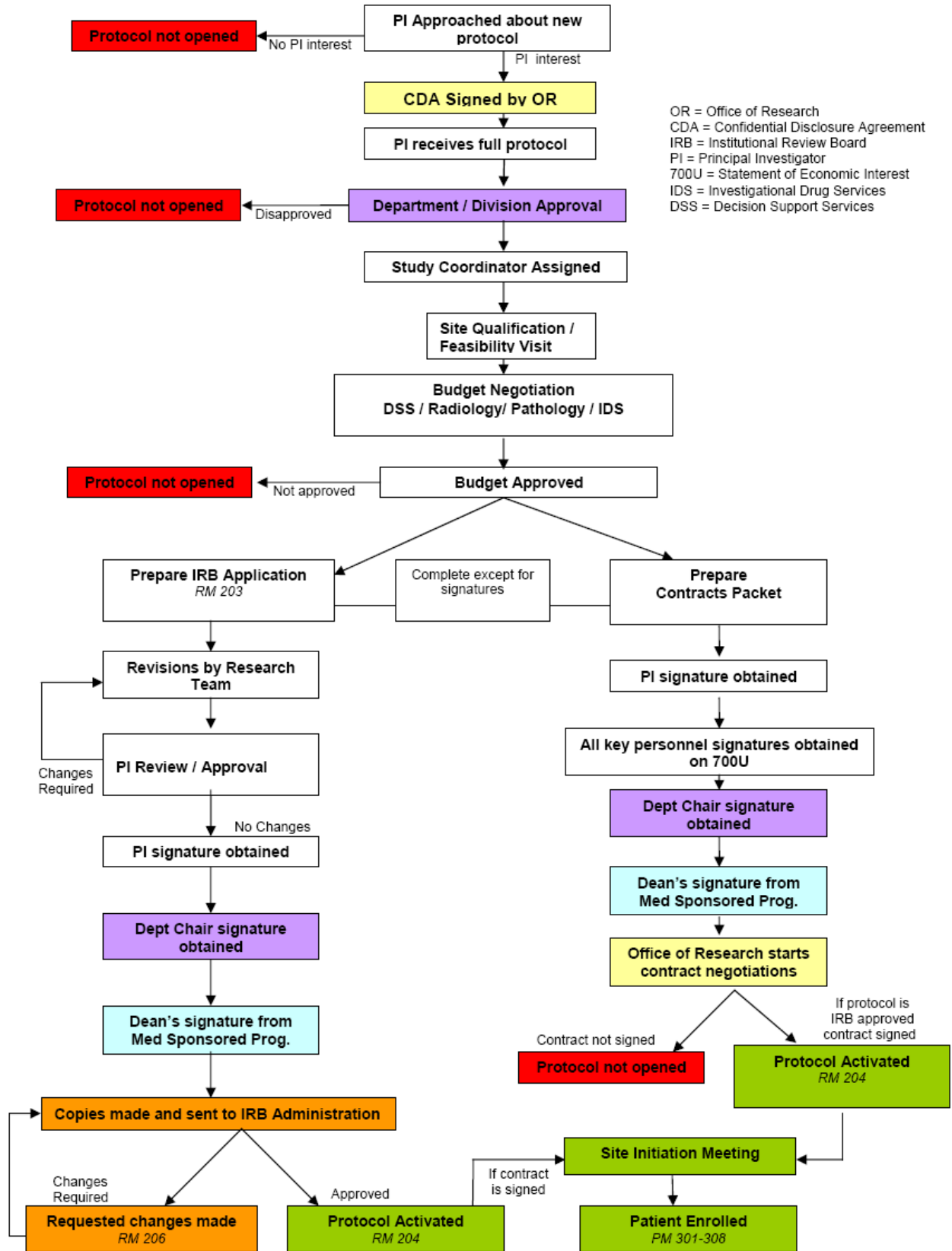
#### D. Contracts Packet

Generally, each new industry-sponsored and investigator-initiated clinical trial proposed by a principal investigator (PI) will need a contract negotiated between the sponsor and the PI. At UC Davis, the Office of Research, Sponsored Programs Office is charged with the responsibility of contract negotiation. When the PI is a School of Medicine faculty member, the submission is processed by the School of Medicine's (SOM) Office of Sponsored Programs before being reviewed by the UC Davis Office of Research (OR). This review process serves to ensure conformity to School of Medicine, University, state, federal, and private agency policies and procedures. Additional information about the services offered by the SOM's Office of Sponsored Programs can be found online at <http://medsp.ucdavis.edu>.

#### E. Human Participants Packet (*see SOPs RM 202 and 203 for more information*)

The Institutional Review Board (IRB) is a committee consisting of UCDCMC physicians, hospital personnel and non-scientific community members. UCDCMC has several committees that review human participant protocols for approval or modification before any research-related procedures can be conducted. The IRB Administration reports to the Associate Vice Chancellor for Research. All new studies, annual renewals of studies, adverse/serious event reports, and modifications/revisions from the study sponsor must be presented to the IRB.

## CLINICAL TRIAL PROTOCOL APPROVAL FLOW



### **3. SCOPE**

This SOP provides an overview of the study preparation for all UCDHS clinical trials.

### **4. RESPONSIBILITY**

All personnel are responsible for understanding and adhering to this preparation process.

**RM 201**  
**CLINICAL TRIAL REGULATORY OVERVIEW**

SOP: RM 201 Version No: 1 Effective Date: 5/10/2007	REGULATORY MANAGEMENT	Supercedes version No: N/A
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Originated by: Cancer Center CTSU

Modified by: CTSC SOP Advisory Panel

Approved by: Translational Research Integration & Compliance Committee

Approval date: 5/10/07

Expiration date: 5/10/09

## **RM 202**

### **INTRODUCTION TO IRB ADMINISTRATION**

#### **1. PURPOSE**

The IRB Administration is a component of the Office of Research (OR) that provides administrative support and record-keeping functions for the Institutional Review Board (IRB).

The 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 the University of California, Davis. The intent is to ensure compliance with the appropriate regulations and policy, and is designed to ensure that the safety and welfare of subjects is properly protected. UC Davis has four IRB committees: two clinical, one social and behavioral and one central IRB (cIRB). Members of each committee include UC Davis faculty, clinicians, staff, students, and community members. The IRB reports to the Vice Chancellor for Research. Contact the IRB at:

IRB Administration  
CTSC Building, UC Davis Medical Center  
2921 Stockton Blvd.,  
Suite 1400, Room 1429  
Sacramento, CA 95817  
tel: (916) 703-9151  
fax: (916) 703-9160

#### **2. PROCEDURE**

##### **A. Research Involving Human Subjects**

Research involving human subjects, as defined by federal regulations, includes any systematic investigation that is designed to develop or contribute to generalized knowledge, and which uses living humans or identifiable private information about humans. Examples of research involving human subjects conducted at UC Davis are drug/device comparison trials, disease prevention studies, ethnographic interviews, psychology experiments, and curricular evaluation studies.

##### **B. Principal Investigator Eligibility**

At UC Davis, faculty members with paid appointments of 50% or more of fulltime may serve as principal investigator (PI) on research involving human subjects. In certain situations, students may assume the role of PI as long as they have a faculty sponsor who fulfills the PI eligibility criteria and who will serve as co-investigator and faculty advisor on the study.

##### **C. Education Requirements**

As of October 1, 2000, the NIH required education on the protection of human research participants for all investigators submitting NIH applications for grants or proposals for contracts. This also applies to new as well as non-competing awards for research involving human subjects. In keeping with this requirement, and in accordance with our Multiple Project Assurance of Compliance which states that federal requirements will be met for

federally sponsored research, as well as other human subjects research regardless of sponsorship, effective October 1, 2000, the IRB has required that, regardless of the sponsor, all personnel listed on human subjects protocols complete the IRB approved educational on-line tutorial program available through the IRB Administration web site. *Please see the IRB Administration Web site for information about completing the required tutorials.*

#### D. IRB Submissions

- i. Please see the remainder of the Regulatory Management Section for policies and procedures related to IRB submission/review and form completion.
- ii. Protocol submission deadlines for committee review are posted on the IRB Administration Web site.
- iii. Protocols must be received no later than 5:00 pm on the deadline day. Any protocol received after the deadline will be automatically placed on the next deadline schedule.
- iv. Committees "A" and "B" review research that is primarily biomedical or clinical in nature.
- v. Committee "C" reviews any research that is primarily social or behavioral in nature.
- vi. Committee "D" reviews all cancer studies approved by a central IRB.
- vii. Applications should be submitted to the IRB Administration.

### 3. SCOPE

This SOP applies to all employees and specifies the policies of IRB Administration.

### 4. RESPONSIBILITY

The Regulatory Coordinator/CRC (if applicable) and Principal Investigator assigned to the study are responsible for ensuring all submissions to the IRB occur in accordance with IRB guidelines.

### 5. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 56.110

45 CFR 46.101 (b)

45 CFR 46.110

UC Davis IRB Administration Web Site: <http://ovcr.ucdavis.edu/home.cfm?id=OVC,1>

## INTRODUCTION TO IRB ADMINISTRATION

SOP: RM 202 Version No: 1 Effective Date: 5/10/2007	REGULATORY MANAGEMENT	Supercedes version No: N/A
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Originated by: Cancer Center CTSU

Modified by: CTSC SOP Advisory Panel

Approved by: Translational Research Integration & Compliance Committee

Approval date: 5/10/07

Expiration date: 5/10/09

## **RM 203.2 CONSENT**

### **1. PURPOSE**

The informed consent form (ICF) provides the participant with a written explanation that will help them decide whether to volunteer to participate in a UCDHS clinical trial.

### **2. PROCEDURE**

#### **A. Informed Consent Form**

- i. The UC Davis informed consent form (ICF) template should be reviewed often on the IRB Administration's Web site, as the standard UC Davis Consent language is updated frequently. Bolded language in the model consent form is mandatory language. Most study sponsors will also have a model consent form, which they require to be incorporated into our UCD standard consent format. It is suggested that the person creating the consent integrate the sponsor model consent into the UC Davis model consent so that no vital information regarding the study is accidentally omitted. However, the UC Davis Institutional Review Board has final jurisdiction over what is contained in the informed consent document.
- ii. If no model consent has been provided, the protocol, along with the investigational drug brochure, will serve as the source for the information required in the consent. If the protocol and the investigator brochure are used as the source, particular attention will need to be paid to the use of non-technical (7<sup>th</sup> grade) language.
- iii. Attach the Experimental Subject's Bill of Rights (numbered as page 1) to all patient consent forms. This document can be found on the IRB Administrations Web site at <http://research.ucdavis.edu>.

#### **B. Elements of the Informed Consent Form**

##### **i. Purpose**

Explain succinctly and simply why the prospective subject is eligible to participate. If subjects must be patients with a specific disease/condition, or receiving care in a certain clinic, say so in clear terms. State clearly what the study is designed to discover or establish. If the study involves a drug, describe the drug in layman's terms, noting whether the drug is experimental or approved by the FDA. State total accrual goal at UCD; if it is a multi-site study, also list total number of subjects study-wide.

ii. Procedures

List procedures and tests and their frequency. Include the location of the study. State whether a patient will be at home, in the hospital, or in an outpatient setting. Describe the procedures chronologically using lay language, short sentences and short paragraphs. The use of subheadings will help to organize this section and increase readability. Define and explain medical and scientific terms the first time they are used in ordinary language. If there are blood draws, explain specifically how much will be taken (use lay terms, e.g., “teaspoons” of blood) and describe for what purpose will the blood be used. Add information regarding pregnancy testing for women of childbearing potential, if required. Indicate the frequency of pregnancy testing. Birth control measures for the study should be described. For randomized studies, list the study groups and under each describe categories of procedures. If objectives include a comparison of interventions, list all procedures, even those considered standard. If a patient will receive a placebo, this must be stated in this section with rationale for administering placebo. Include a statement (in 7<sup>th</sup> grade language) about double-blinding, cross-over studies, randomization studies, as applicable.

Procedures should be listed under two headings: 1) procedures that are part of regular care and may be done even if the participant does not join the study (list tests and procedures as appropriate) and 2) procedures that are not part of regular care and will only be done if the participant joins the study. Identify any procedures that are experimental, not validated, or unproven (e.g., experimental drugs, experimental therapy, etc.). Refer to the protocol for specific treatment and response assessment procedures.

Patients must know how long they will be in the study, separated into time spent in the treatment portion of the study and time spent in follow-up. It is usually emphasized that follow-up is a standard of care for all patients when applicable.

Provide an easy to follow table of study procedures.

Describe the circumstances that would require investigators to terminate the participation of particular participants. For example, participant experiencing an adverse event, not benefiting from the research, or non-compliance with the research protocol. Some studies involve medications or procedures that would be dangerous for subjects to discontinue abruptly. Provide subjects with information on the consequences of withdrawal, including descriptions of the procedures regarding how to withdraw safely from the research (e.g., follow-up physical exam, lab work, etc.).

iii. Risks

The suggestion is to organize side effects into table format in order or likely, less likely, rare, etc. if the sponsor model consent provides this kind of stratification. Table formats are easiest for patients to read. Ensure that the page break does not disrupt the format. Risks must be listed exactly as they are in the sponsor model consent form/ or the study protocol if a model consent form is not provided.

iv. Benefits

Describe the anticipated benefits to subjects resulting from their participation in the research. Include statement that no benefit is guaranteed. State anticipated benefits, if any, to science or society expected from the research.

v. Alternatives

Describe appropriate alternative procedures or courses of treatment or therapy that may be advantageous to the subject.

vi. Confidentiality

Include standard IRB consent language regarding confidentiality. Give a brief description of how personal information, research data, and related records will be coded, stored, etc. to prevent access by unauthorized personnel. If applicable, state if and when individual responses to survey questionnaires will be destroyed, following data analysis. If the research involves a drug with an IND or a medical device with an IDE, this section must include information that the FDA has the authority to review the research records. Aside from this mandatory language, insert all entities that may audit the study (sponsor, IRB, etc.).

vii. Emergency Care and Treatment For Injury

The following statement is mandatory for all submissions sent to the UC Davis IRB. Do NOT modify the following language or add any additional language to the consent form regarding subject injury:

*If you are injured as a direct result of research procedures, you will receive reasonable necessary treatment at no cost. The University of California does not provide any other form of compensation for injury.*

viii. Costs

In the IRB model consent there are various options for possible cost language. Please consult with your study sponsor/budget for *exact* details as to what is and is not covered by the study and what will be charged to the patient's insurance carrier.

ix. Compensation

Describe the payment the subject is to receive for participation. Completing the research may not be made a condition of payment. If no compensation is offered, include statement that subject will not receive compensation for participation.

If samples will be taken for research and development purposes not related to the subject's treatment or condition (which includes all samples collected for *future* research, as will be specified by the study protocol), include standard IRB language regarding property rights and ownership interests.

x. Right To Refuse or Withdraw

Include standard IRB language about subjects' rights to refuse or withdraw from the study. Also, include a statement that significant new findings that may affect the subject's health or willingness to continue in the study will be provided.

xi. Principal Investigator's Disclosure of Personal and Financial Interest In the Research and Study Sponsor

Include information about whether the investigator does or does not have a personal or financial interest in the study. *(The latter generally encompasses all research conducted at the UC Davis Cancer Center)*

xii. Questions

Include standard language Include contact information for the investigators (including 24-hour emergency number).

Include standard IRB consent language regarding contacting the IRB Administration for questions regarding participant rights and research study participation.

xiii. Consent

Include standard language.

*My signature below will indicate that I have decided to participate in this study as a research subject. I have read and understand the information above. I understand that I will be given a signed and dated copy of this consent form and the Bill of Rights.*

_____	_____	_____
<i>Signature of Subject or Legal Representative</i>	<i>Date</i>	<i>Time</i>
_____	_____	_____
<i>Signature of Investigator</i>	<i>Date</i>	<i>Time</i>

### 3. SCOPE

This SOP specifies the guidelines for writing the informed consent form for all UCDHS clinical trials.

### 4. RESPONSIBILITY

The Clinical Research/Regulatory Coordinator is responsible for writing the informed consent document prior to submission to the IRB. The Principal Investigator is ultimately responsible for the study and the informed consent process.

**RM 203.2  
CONSENT**

SOP: RM 203.2 Version No: 1 Effective Date: 5/10/2007	REGULATORY MANAGEMENT	Supercedes version No: N/A
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Originated by: Cancer Center CTSU  
Modified by: CTSC SOP Advisory Panel  
Approved by: Translational Research Integration & Compliance Committee  
Approval date: 5/10/07  
Expiration date: 5/10/09

## **RM 204 STUDY ACTIVATION**

### **1. PURPOSE**

Once the Institutional Review Board (IRB) packet and/or the Contracts packet have been approved, a few steps remain that must be completed before participants can be enrolled and the study can be considered active.

### **2. PROCEDURE**

#### **A. DaFIS Account Establishment**

When the Clinical Trials Agreement (CTA) or contract has been approved and signed by the Office of Research and the sponsor, the signed contract will be forwarded to the responsible department for establishment of a seven digit DaFIS account. This number is used in the Financial Information System to identify each revenue (income), expenditure (expense), or balance sheet account authorized in the accounting records. Account numbers are assigned by, and unique to, the department to which they belong.

The department will forward an Extramural Award Notice to the Principal Investigator (PI) notifying him/her of the DaFIS account number established. This form must be signed by the PI and returned to the account manager.

#### **B. Bulk Account Establishment**

If the clinical trial will require any procedures (including lab draws) that will not be billed to the patient, a hospital bulk account will need to be opened.

- i. Obtain a "Bulk Account Application for Hospital Billed Charges" and complete all required sections.
  - a. DaFIS Account number
  - b. The "prepared by" line should be signed by the person completing the form.
  - c. The first "reviewed by" line should be signed by the study PI.
  - d. The second "reviewed by" line should be signed by the applicable department manager.
  - e. The third "reviewed by" line should be left blank.
- ii. The signed form should be faxed to Patient Accounts Analysis (number is on the form).
- iii. Once Patient Accounts Analysis has processed the form, you will receive a copy of the finalized form and a letter assigning your bulk account number and explaining the basics of how a bulk account works.
- iv. The bulk account is now ready for use.

#### **C. Department of Radiology Research Procedure Form**

If the clinical trial will require radiology exams (e.g. x-rays, CT scan, MUGAs, etc) that will not be billed to the patient (i.e. are not standard of care), a pink Department of Radiology Research Procedure Request Form will need to be completed.

- i. Once a bulk account number has been assigned, complete the Department of Radiology Research Procedure Request Form.
- ii. Fax the completed form to 734-6548.
- iii. Once Radiology has processed the form you will receive a copy of the request form signed by the Radiology Research Vice Chair and Imaging Manager. You will also receive an email confirmation that will include CPT codes and research billing rates for all requested exams.

#### D. CTSC Clinical Research Center (CCRC)

The Clinical and Translational Science Center's Clinical Research Center (CCRC) is a highly specialized patient unit that provides investigators with opportunities for careful study of disease. This NIH-funded facility is a joint partnership between the UC Davis Health System and the Veterans Affairs Northern California Health Care System. CCRC resources include specialized research nurses, research dietitians, biostatisticians, computer hardware and software systems for data management and analysis, and sophisticated laboratories for both inpatient and outpatient research.

The CCRC is available to any member of the faculty, residents, postgraduate fellows, medical students, nurses, research coordinators and support staff in any department of the UC Davis Health System and the Veterans' Affairs. Use of the Center is justified on the basis of three criteria: (1) the quality and significance of the research, (2) the special need for the Center's unique facilities, and (3) the common usefulness or collective justification for facilities or personnel.

- i. Protocols considering the use of the CCRC can be reviewed by either IRB Committee A or B.
- ii. Once IRB approval has been obtained, a 'CTSC Application for Use' must be completed (see CTSC Web site for application). The CTSC's Resource Review Committee will then determine if the protocol falls within the CCRC's scope of research interest.
- iii. If the Review Committee grants approval, the research coordinator and PI will meet with the CCRC Nurse Manager prior to treating any participants at the CCRC. Protocol-specific procedures and all CCRC services to be utilized will be outlined at this meeting.
- iv. For more information about the CCRC, please visit the CTSC Web site at <http://www.ucdmc.ucdavis.edu/ctsc>

#### E. Operating Room Resource Review

If the clinical trial will require the use of a UCDHS operating room, an Operating Room Resource Review Approval Letter must be on file before research can begin.

- i. Complete the top portion of the Operating Room Resource Review Approval Letter.
- ii. Submit the complete approval letter plus a full copy of the protocol to the Operating Room Manager.
- iii. Once the signed approval letter is received, forward a copy to the School of Medicine Office of Sponsored Programs.

### **3. SCOPE**

This SOP applies to the research team and specifies the final steps of study activation that must occur before a patient can be enrolled in a UCDHS clinical trial.

### **4. RESPONSIBILITY**

The Clinical Research/Regulatory Coordinator, with the oversight of the Principal Investigator, is responsible for ensuring the above procedures are completed, when applicable, before any participants are enrolled in the approved clinical trial

### **APPLICABLE REGULATIONS AND POLICIES**

UC Davis Health System policy 1502

UC Davis Health System policy 1815

**RM 204  
STUDY ACTIVATION**

SOP: RM 204 Version No: 1 Effective Date: 5/10/2007	REGULATORY MANAGEMENT	Supercedes version No: N/A
---	--------------------------	-------------------------------

Originated by: Cancer Center CTSU

Modified by: CTSC SOP Advisory Panel

Approved by: Translational Research Integration & Compliance Committee

Approval date: 5/10/07

Expiration date: 5/10/2009

## **RM 205 RENEWALS**

### **1. PURPOSE**

An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year (45CFR46.109). A study must have annual approval until the study is completed and data submission requirements are terminated; or all patients registered to the study at UC Davis have expired.

### **2. PROCEDURE**

#### **A. Overview**

Four months prior to the renewal date, the IRB will send the Principal Investigator (PI) a courtesy notice (commonly referred to as the "blue sheet" - Template RM-C) advising that the study is due to expire. The notice will include an administrative due date. This document cannot be relied upon to inform the study staff of the upcoming expiration, each unit should devise a tracking document listing each protocol's expiration date. The regulatory process must be completed in its entirety and submitted to the IRB prior to the administration due date to ensure approval prior to the study's expiration date.

- i. The PI will forward the blue sheet to the study coordinator or designee.

#### **B. Progress Report**

For more information, please refer to the IRB's blue sheet which will have the most recent version of the Progress Report template used for completion of the renewal process. If you do not receive a blue sheet, please contact the IRB Administration and request that one be sent to you.

Information for the progress report is obtained through a number of source documents:

- Previously submitted renewal packets.
- Sponsors' websites, and /or report of studies.
- CRCs who have subjects enrolled on the study.

#### **C. Consent**

- i. Along with the completed progress report you will need to include a copy of the most recently approved IRB consent form (stamped version).
- ii. If updates are necessary at the time of renewal, highlight those changes
- iii. Include a clean version of the consent to be stamped with IRB approval date stamp.

**NOTE:** AS A GENERAL RULE, MODIFICATIONS/AMENDMENTS SHOULD NOT BE MADE AT THE TIME OF ANNUAL RENEWAL. IF CHANGES ARE REQUIRED THEY SHOULD BE SUBMITTED SEPARATELY AS A MODIFICATION/AMENDMENT.

#### **D. Description of Study (DOS)**

- i. Along with the completed progress report, you will need to include a copy of the most recently approved IRB DOS.
- ii. If updates are necessary at the time of renewal, highlight those changes.
- iii. Include a clean version of the consent to be stamped with IRB approval date stamp.

**NOTE:** AS A GENERAL RULE, MODIFICATIONS/AMENDMENTS SHOULD NOT BE MADE AT THE TIME OF ANNUAL RENEWAL. IF CHANGES ARE REQUIRED THEY SHOULD BE SUBMITTED SEPARATELY AS A MODIFICATION/AMENDMENT.

#### E. Modifications/Amendments

Copies of all IRB approvals for modifications that occurred during the renewal period must be included with the renewal application.

#### F. Unanticipated Problem Table (Adverse Events)

A summary of all internal and external adverse events that occurred at UCD and other sites since the last renewal period..

- i. The appropriate CRC should prepare the Adverse Event table to ensure it accurately reflects the AE activity related to the study during the renewal period.
- ii. Attach a DSMB report if one is available.

#### G. Other Supporting Documents

- i. A summary of any recent literature related to the study.
- ii. If applicable, attach reports from the sponsor.
- iii. If the study was audited during the past year, provide all documentation between PI and the auditor.
- iv. In a tabulated format, report all minor and major deviations during the past year, with date of occurrence, impact on subject safety and resolution.

### 3. SCOPE

This SOP specifies the guidelines for preparation of the annual renewal submissions to the IRB.

### 4. RESPONSIBILITY

The Study Coordinator or designee is responsible for preparing and reviewing the renewal packet.

### 5. APPLICABLE REGULATIONS AND GUIDELINES

45CFR46.109e  
UCDHS Policy and Procedure 1507

**RM 205  
RENEWALS**

SOP: RM 205 Version No: 1 Effective Date: 5/10/2007	REGULATORY MANAGEMENT	Supercedes version No: N/A
---	--------------------------	-------------------------------

Originated by: Cancer Center CTSU

Modified by: CTSC SOP Advisory Panel

Approved by: Translational Research Integration & Compliance Committee

Approval date: 5/10/07

Expiration date: 5/10/09

## **RM 206 RESPONSE TO IRB CONCERNS**

### **1. PURPOSE**

The purpose of this document is to provide an overview of the process for submitting requested revisions to the Institutional Review Board (IRB). Revisions to a protocol or consent fall under the category of either Minor Revisions/Clarifications or Serious Concerns/Revisions. Once the protocol has been reviewed by the IRB, the Principal Investigator (PI) will receive a letter (Notice of Action) within 5-10 working days. The PI is asked to address IRB concerns as soon as possible, and no later than 30 days from the date of notification. Failure to do so will result in return of the submission packet to the PI with no Committee action.

### **2. PROCEDURE**

#### **A. Minor Concerns/Revisions**

- i. The Clinical Research Coordinator (if applicable), in collaboration with the PI, drafts a memo to the IRB addressing all issues raised by the Committee. The memo must be submitted to the IRB along with copies of the revisions and the Notice of Action. The changes made to these forms must be highlighted, bolded or underlined. Two copies of all the above-mentioned documents must be submitted. Minor revisions are submitted for review to the Committee Chair; full IRB review is not required
- ii. Once the revisions have been reviewed by the Chair of the Committee, the protocol will be processed for final approval. Approval documents are then issued to the PI.

#### **B. Serious Concerns/Revisions**

- i. Serious concerns/revisions are submitted for full review to the Committee.
- ii. The CRC (if applicable), in collaboration with the PI, drafts a memo to the IRB addressing all issues raised by the Committee. The memo must be submitted to the IRB along with copies of the revisions and the Notice of Action. The changes made to these forms must be highlighted, bolded or underlined. Twenty-four copies of all the above-mentioned documents must be submitted.

### **3. SCOPE**

This SOP specifies the procedure for submitting revisions requested by the IRB at the time of submission of a new protocol, or at the time of a renewal.

### **4. RESPONSIBILITY**

The Principal Investigator (PI) receives the notification of clarification/concerns and forwards it to a member of the research team (e.g., Clinical Research Coordinator), if applicable, for corrections and responses to the IRB's questions. If a question/concern is beyond the scope of the team member, the PI should help draft a response. The team member will make the necessary copies and re-submit the packet to the IRB for review/approval.

**RM 206**  
**RESPONSE TO IRB CONCERNS**

SOP: RM 206 Version No: 1 Effective Date: 5/10/2007	REGULATORY MANAGEMENT	Supercedes version No: N/A
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Originated by: Cancer Center CTSU

Modified by: CTSC SOP Advisory Panel

Approved by: Translational Research Integration & Compliance Committee

Approval date: 5/10/07

Expiration date: 5/10/09

## RM 207 MODIFICATIONS, AMENDMENTS AND REVISIONS

### 1. PURPOSE

Any changes to a research plan (protocol) must be submitted to the Institutional Review Board (IRB) for review and approval prior to implementation of such a change. This includes changes in personnel, interventions, inclusion/exclusion criteria, location of research, side effects, advertisements for the recruitment of subjects and change in number of subjects. Depending on the proposed change(s), the modification may be reviewed by the IRB Chair only or submitted for full committee review (this is decided by the IRB). Requests for modifications can be made to the IRB at any time by memorandum, making reference to the protocol number, PI and title of study.

### 2. PROCEDURE

#### A. Request for modification

- i. The *Request for Modification/Amendment* form is available on the IRB Administration's Web site.
- ii. Each *Request for Modification/Amendment* form must contain the following:
  - a. A date line with the current day's date.
  - b. Line with the appropriate protocol version date.
    - If the modification/amendment involves a change to the protocol version, the new protocol version date should be entered.
    - If the modification/amendment does not involve a change to the protocol version the currently approved protocol version date should be entered.
  - c. Line with the appropriate consent document version date.
    - If the modification/amendment involves a change to the consent document the new consent version date should be entered.
      - \* *Note: Any change to the protocol version date will require changes to the consent documents footer and a revised copy must be submitted as part of the modification request packet.*
    - If the modification/amendment does not involve a change to the consent document the currently approved consent version date should be entered.
  - d. Line with the appropriate description of study (DOS) version date.
    - If the modification/amendment involves a change to the DOS version the new DOS version date should be entered.
      - \* *Note: Any change to the protocol version date will require changes to the consent documents footer and a revised copy must be submitted as part of the modification request packet.*
    - If the modification/amendment does not involve a change to the DOS version the currently approved DOS version date should be entered.
- iii. Two copies of the *Request for Modification/Amendment* form must be submitted to the IRB Administration.
- iv. Two copies of all supporting documentation (e.g., sponsor's revised Investigator's Brochure, revised DOS, Consent, etc.) must be submitted with the *Request for Modification/Amendment* form

## B. Protocol

- i. If information in the protocol is to be changed, all changes must be highlighted. If it is not possible to highlight the changes in the protocol, the changes must be outlined in a cover letter.
- ii. The IRB receives a highlighted copy and a “clean” copy without the highlighting.
- iii. The footer should indicate the new version of the protocol.

## C. Consent

- i. If the proposed change effects the information to be given to the subjects, two copies of the revised Informed Consent Form must also be submitted. All changes and additions must be highlighted on one copy and the other copy should be a “clean” copy without the highlights.
  - ii. The footer should indicate the same version as the protocol.

## D. Description of Study

- i. Two copies, one highlighted and one clean should also be submitted.
- ii. The footer should indicate the same version as the protocol.

## E. IRB Approval

- i. Once approved, copies should be made of the approved modification, protocol, consent and description of study (DOS).

Note: If there are substantial changes in the study, the existing protocol will need to be closed and it will be necessary to fill out a new Full Committee Review Application, obtain required signatures, and submit for full committee review.

## 3. SCOPE

This SOP specifies the guidelines for the process of submitting requests for modification to the IRB.

## 4. RESPONSIBILITY

A member of the research team (e.g., Clinical Research Coordinator) is responsible for preparing and assembling the documentation, making necessary changes to the documents, and submitting the documents to the IRB Administration. The Principal Investigator is ultimately responsible for the conduct of the study.

**RM 207**  
**MODIFICATIONS, AMENDMENTS AND REVISIONS**

SOP: RM 207 Version No: 1 Effective Date: 5/10/2007	REGULATORY MANAGEMENT	Supercedes version No: N/A
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Originated by: Cancer Center CTSU

Modified by: CTSC SOP Advisory Panel

Approved by: Translational Research Integration & Compliance Committee

Approval date: 5/10/07

Expiration date: 5/10/09

## **RM 208 STUDY CLOSURE**

### **1. PURPOSE**

When study sponsors/or investigators decide to close protocols they may do so in a variety of ways and for a variety of reasons. A study may be closed to accrual, but remain open to follow-up, a study may be closed temporarily or a study can be closed to the IRB permanently when there are no living patients, or when the protocol objectives have been met. Regardless of why the study is closed, all closures must be reported to the IRB Administration and documents must be organized for storage.

### **2. PROCEDURES**

#### **A. Closed to Accrual but Open to Follow-up**

- i. The sponsor generally sends notification when a study has met accrual goals or protocol objectives.
- ii. A memo is sent to the IRB when a protocol is closed to accrual. The study remains open for annual IRB renewal as long as data is being submitted.
- iii. At the time of annual renewal, the protocol is renewed for follow-up purposes only. All procedures are followed for the renewal, however, in the Progress Note, a statement is made that the protocol is closed to accrual and date of closure is noted. (See RM 103).

#### **B. Temporary Closure**

- i. The sponsor sends notification when a study is temporarily closed for reasons of toxicity analysis, interim analysis or any reason to put a study on hold.
- ii. A memo is sent to the IRB stating protocol is closed temporarily. Give the reason for closure (i.e. toxicity analysis, change in dosing), and submit supporting documentation if applicable.
- iii. Notified the IRB of estimated time of reactivation, and the measures being taken to reactivate.
- iv. When the study is ready to reactivate, the protocol will go through the same procedure for a full committee review (see RM 103).

#### **C. Permanent Closure to IRB**

- i. A protocol may be permanently closed to the IRB if one of the following occurs:
  - a. The sponsor sends notification that a study is complete (terminated) and that further data collection is no longer required.
  - b. All subjects have completed all study visits and follow-ups or are deceased.

#### **D. Industry Sponsored Close-Out**

- i. Complete all CRF and source documents.
- ii. In most cases the sponsor will want to complete a close out visit to collect any outstanding CRFs and data.
- iii. Complete all requests for data corrections or verifications on the CRF.
- iv. All remaining drugs are collected from study subjects (if appropriate for investigational drug and inventory all used and unused drugs).
- v. The used and unused drug supplies are destroyed or returned to the Sponsor in the manner specified by the sponsor. Shipping documentation must be retained if drug returned to the sponsor.
- vi. Copies of the drug logs, final inventory and return documents are filed in the regulatory binder.
- vii. All other sponsor required reports are completed. A copy is filed in the regulatory binder.
- viii. The PI or designee completes memo to the IRB indicating closure/final and provides a short narrative summary, similar to the annual progress report, of the conclusion of the study to the IRB. A copy of the report is sent to the Sponsor and filed in the regulatory binder.
- ix. Review the regulatory binder and recover any missing documents or place a note to file or waiver (if granted by sponsor) in the binder.
- x. Store all applicable study documentation as required by the Sponsor.
  - Per 21 CFR 312.6(c) the FDA requires that all study documents are maintained for either 2 years after the marketing application (NDA) is approved for the indication investigated or 2 years after the Sponsor notifies the FDA that the investigation for the indication has been discontinued.
  - Sponsor requirements may be vary, please refer to protocol and sponsor for additional information.
- xi. Document completion of study participation in the subject's research/medical records.
- xii.

### **3. SCOPE**

This SOP specifies the ways a study can be closed, and the procedure for notifying the IRB and pharmacy of protocol closure.

### **4. RESPONSIBILITY**

The Research Coordinator or research administrator is responsible for preparing memo notices for IRB submission, for contacting the Investigational Pharmacy, if applicable, and for assembling documentation if required by the study sponsor. The Research Coordinator is responsible for

Date of version: 5/10/07  
Replaces previous version: N/A

printing all documentation for the IRB, the research records, the regulatory files, and the study sponsor.

The PI is responsible for ensuring that the study is closed out according to applicable regulations.

**RM 208  
STUDY CLOSURE**

SOP: RM 208 Version No: 1 Effective Date: 5/10/2007	REGULATORY MANAGEMENT	Supercedes version No: N/A
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Originated by: Cancer Center CTSU

Modified by: CTSC SOP Advisory Panel

Approved by: Translational Research Integration & Compliance Committee

Approval date: 5/10/07

Expiration date: 5/10/09

## RM 209 SPONSOR MONITORING VISITS

### 1. PURPOSE

The monitoring visit for a clinical trial is to resolve any problems, answer questions, review treatment, protocol compliance and source documentation. Monitoring is distinctly different from an audit. The monitor may be a physician, nurse or CRC who represents the pharmaceutical company/sponsor. The monitor may not change any documentation in your case report forms (CRFs) but can request you to change entries. Case report forms after review and correction are then taken back to the pharmaceutical company/sponsor for analysis.

### 2. PROCEDURE

#### A. Preparation

- i. Notify PI and research administrator, if applicable, that monitoring visit has been scheduled.
- ii. Check with Investigational Drug Services (IDS) Pharmacy for Drug Log if investigational or sponsor provided drug is involved. If the monitor wants to visit the IDS Pharmacy, call #703-4093 to set up an appointment.
- iii. Order Hospital Medical Records for each patient to be reviewed.
  - Charts should be ordered through EMR. If a large number of charts are needed, they can be picked up at Health Information Management (HIM).
  - If only one or two charts are needed, charts should be ordered through EMR and can be delivered

#### B. Monitor Arrival

- i. Upon arrival, the CRC should request that the study monitor sign in using a Sign-in Log. *This log is maintained for audit purposes.*

#### C. Regulatory Files

- i. The regulatory files should be ready and available for review when the monitor arrives. The regulatory files should include the following:
  - Current copies of IRB approvals
  - Regulatory documents
  - Correspondence

#### D. Patient Data

- i. Current data should be appropriately entered on the study Case Report Forms (CRFs) and ready for review.

- ii. Source documentation for all entries in the study research record and CRFs must be available for review.

### **3. SCOPE**

This SOP applies to all clinical research monitoring visits at UCDHS

### **4. RESPONSIBILITY**

The Clinical Research Coordinator, or designated research team member, is responsible for ensuring that all procedures outlined above are followed.

### **5. APPLICABLE REGULATIONS AND GUIDELINES**

21CFR 312.56

**RM 209**  
**SPONSOR MONITORING VISITS**

SOP: RM 209 Version No: 1 Effective Date: 5/10/2007	REGULATORY MANAGEMENT	Supercedes version No: N/A
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Originated by: Cancer Center CTSU

Modified by: CTSC SOP Advisory Panel

Approved by: Translational Research Integration & Compliance Committee

Approval date: 5/10/07

Expiration date: 5/10/09

## **RM 210 FEDERAL, REGULATORY AND SPONSOR AUDITS**

### **1. PURPOSE**

According to the guidelines of Good Clinical Practice (GCP), an audit is a systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures, good clinical practice and the applicable regulatory requirements.

Site audits can occur for a variety of reasons. Audits can be routine, triggered by a pending New Drug or Premarket Application (NDA or PMA), or triggered by complaints from a study participant and/or research personnel. Regardless of the reason behind the audit, specific procedures need to be followed when preparing for an audit and on the day of the audit.

### **2. PROCEDURE**

#### **A. Audit Preparation**

*Note: For Food and Drug Administration (FDA) audits, reasonable notice must be given. In most cases, "reasonable" notice will be approximately a week.*

- i. For FDA or for-cause audits, notify the UCDHS Research Compliance Officer, located in the Clinical and Translational Science Center (CTSC), at 916-703-9122.
- ii. Notify the Principal Investigator (PI) and all key study personnel of the audit and ensure they will be available if necessary.
- iii. If investigational or sponsor-provided drug is involved, contact the Investigational Drug Services (IDS) Pharmacy and request copies of all drug accountability logs.
- iv. Order Hospital Medical Records for all audited patients.
  - a. If a large number of charts are needed, call the Health Information Management Manager at 916-734-5209 to inform him/her of the upcoming audit and request the charts be delivered directly to your unit.
  - b. If only one or two charts are needed, charts should be ordered through EMR.
- v. Ensure that all regulatory documents and participant research records are accessible, complete, and well organized. If the study has been closed for some time, these records may need to be retrieved from storage.
- vi. If the audit will involve a tour of any UCDHS facilities, the applicable department and/or personnel must be notified as soon as possible.

## B. Auditor Arrival

- i. If the auditor is from the Food and Drug Administration (FDA), the auditor should present a Form FDA 482 Notice of Inspection, FDA credentials and photo identification. If the auditor does not immediately present these items, a member of the research team should request to see them. *Note: A site may be cited for not requesting to see these documents.*
- ii. Upon arrival, a member of the research team should request that the auditor sign in using a Sign-in Log.
- iii. If possible, a member of the research team should remain with the auditor whenever he/she leaves the assigned auditing space.

## C. Study Documents

- i. All study documents must be ready and available for review when the auditor arrives. The study binder should include the following:
  - Current copies of all IRB approvals
  - Regulatory documents
  - Correspondence
- ii. Current data should be appropriately entered on the study Case Report Forms (CRFs) and ready for review.
- iii. Source documentation for all entries in the study research record and CRFs must be available for review.

## D. During the Audit

- i. Document access will be limited to the study of interest.
- ii. If the auditor requests copies of documents, they should be made available to him/her.
- iii. Research personnel may not sign any audit-related documents. If the auditor requests signature, inform them that documents must be reviewed by management and/or counsel before being signed.
- iv. Ensure understanding before answering a question. Answers should be polite and concise. Do not withhold information.
- v. When the answer to a question is unknown, defer to the most appropriate person.

## 3. SCOPE

This SOP applies to all federal, regulatory or sponsor audits related to UCDHS clinical trials.

#### **4. RESPONSIBILITY**

The research team is responsible for ensuring that all procedures outlined above are followed. The PI is ultimately responsible for the conduct of the study.

#### **5. APPLICABLE REGULATIONS AND GUIDELINES**

UCDHS Policy and Procedure 1506

**RM 210**  
**FEDERAL, REGULATORY AND SPONSOR AUDITS**

SOP: RM 210 Version No: 1 Effective Date: 5/10/2007	REGULATORY MANAGEMENT	Supercedes version No: N/A
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Originated by: Cancer Center CTSU

Modified by: CTSC SOP Advisory Panel

Approved by: Translational Research Integration & Compliance Committee

Approval date: 5/10/07

Expiration date: 5/10/09