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***Rebecca and John Moores  
UCSD Cancer Center***

**CLINICAL RESEARCH  
POLICIES AND PROCEDURES  
(2008)**

**MOORES UCSD CANCER CENTER  
CLINICAL RESEARCH POLICIES**

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## **I. INTRODUCTION**

This book is a guide to the services and functions of the Clinical Trials Office and the Protocol Review and Monitoring System at the Rebecca and John Moores UCSD Cancer Center. Part I is intended to help new and established Members of the Center know where to obtain information, advice and assistance when they wish to set up a therapeutic, translational, or non-therapeutic trial based upon a new discovery, an ethically testable hypothesis or a comparison of two clinical regimens. Part II describes protocol preparation guidelines. Parts III and IV of the book explain the operation of the Clinical Trials Office and of the Protocol Review and Monitoring System. Examples of the NCI protocol format, IRB application questions, and other useful forms and information are included as appendices.

### **Clinical Trials Office**

The Moores UCSD Cancer Center is NCI designated and the Clinical Trials Office (CTO) is a Shared Resource of the Center intended to give practical help to investigators wishing to conduct clinical studies.

Services offered by the CTO include assistance with: a) trial design and protocol development, b) submissions to the Protocol Review and Monitoring Committee (PRMC) and the Institutional Review Board (IRB), otherwise known as the Human Research Protections Program (HRPP), of the University, and the Institutional Biosafety Committee (IBC) if required c) budget development, d) project management, e) study coordination and data management, and f) participant recruitment. The CTO will offer as much support as possible from Clinical Research Professionals (CRP: research nurses, clinical research associates (CRAs), and project managers) that it has available, for the actual conduct of the trials. The Office is also an umbrella organization that organizes and coordinates the work of CRPs made available by grants from National Cooperative Groups (e.g. CALGB and NSABP) and the work of CRPs sponsored by drug companies for clinical trials approved by the Center.

### **Protocol Review and Monitoring System**

A Protocol Review and Monitoring System (PRMS) is a requirement of an NCI designated Cancer Center. The Protocol Review and Monitoring Committee (PRMC) has the responsibility for scientific peer review of all cancer-related clinical protocols at UCSD. This is carried out in conjunction with the IRB review of the protocols for human subjects' ethical issues.

It is mandatory that all new cancer related clinical protocols are evaluated for scientific merit by this Committee. Protocols subject to PRMC review include therapeutic and prevention clinical trials, translational research, and non-therapeutic studies which involve participation by human subjects with or at risk for cancer.

PRMC review is conducted in tandem with IRB review, and protocol submission deadlines are the same. Commentary, recommendations, and actions by the PRMC are incorporated into the IRB notice to the investigator and must be addressed before the protocol can be activated. Protocols that are sent only to the IRB will be deferred as a matter of IRB policy until they have been reviewed by the PRMC. Occasional non-therapeutic protocols that involve only collection of existing tissue specimens and do not use Cancer Center resources may be exempted from PRMC scrutiny. If an investigator is not certain whether their protocol requires PRMC review, the PRMC office should be contacted in advance, to avoid unnecessary delays.

### **Procedures for Initiating Clinical Research Protocols:**

- Formulate an idea, hypothesis or specific aims of the study.
- Contact the CTO Academic Director, Tony Reid, MD, PhD , for preliminary advice and directions and to discuss resources that may be needed (CRPs, budget, referrals, collaborators). In the event that Dr. Tony Reid is not available in the timeframe needed, contact CTO Assistant Director, Kirsten Loureiro, MPH.
- Consult with Biostatistics Resource personnel regarding study design, sample size, and plan for data analysis.
- Contact the PRMC chair, Dr. Carlos Carrera, to discuss possible FDA regulatory requirements (IND, adverse event reporting) and IRB issues (required elements of the informed consent, ethical considerations).
- For therapeutic and prevention clinical trials, prepare master protocol in NCI format (see section II for guidelines).
- Prepare IRB application (25 questions) with supplemental GCRC and Biosafety forms if appropriate. Note that the CTO does offer IRB application preparation and submission services but given the nature of a shared resource center and the competing demands placed upon it, the CTO may not be able to accommodate all requests. See section II for details regarding the IRB application template.
- Submit to PRMC and IRB:
  - 1 master protocol, 1 investigator's brochure, and 10 IRB applications to the PRMC office (0698); 3 master protocols, 1 investigator's brochure, and 20 IRB applications to the Human Research Protections Program (0052).
- Respond to IRB/PRMC notification of review if applicable, addressing all questions, comments and requests for protocol or consent modification. The investigator's response is addressed to the IRB. Copies of the investigator's response, modified protocols (in response to committee comments or amendments initiated by investigator/sponsor), and any protocol-related correspondence must be forwarded

to the PRMC Office (0698). To avoid delay in activation of the protocol, the response should be made within 5 working days of receipt of the review notification.

- Industry sponsored studies require a clinical trials agreement (CTA). This agreement requires review and approval by the Clinical Trials Administrative Services and Research Compliance Office (CTAS). The PI, Cancer Center Director, and the Cancer Center Business Office must sign the CTA application before it is sent to the CTAS Office.
- Investigator-initiated protocols supported by a Sponsored Research Agreement (SRA) with a commercial entity are processed through the Office of Contracts and Grants.
- NIH and NIH subcontract proposals for Health Sciences are handled through the Health Sciences Sponsored Projects Preaward Office. Contact Andrea Rollins, Director, (858) 534-2036. Studies initiated by investigators are handled through the Office of Contracts and Grants, contact Carroll Ekberg, Asst Director (858) 534-9884.
- Once approved by the PRMC/IRB and the appropriate contracts/agreements (which include acceptable clinical trial budgets) are signed, the protocol can be activated.
- Seek assistance with CRPs/data management, patient recruitment, etc. from the assigned CTO project managers.
- It is mandatory that all subjects enrolled in a study must be registered with the CTO by entering the subjects into the CTO central database (see section III). A copy of each signed consent form is to be filed with the CTO.
- ALL correspondence on matters such as protocol amendments or adverse events **MUST** be submitted to both the PRMC and the IRB.
- Monitoring of institutional studies are reviewed by the Monitoring Subcommittee which forwards its recommendations to the PRMC for a final determination. This includes a) verification of patient enrollment, b) monitoring of accrual and c) full protocol audits. See section IV for details.

### **Resources for Clinical Research Protocols:**

MCC CTO Academic Director: Tony Reid, MD, PhD	822-4050
MCC CTO Assistant Director: Kirsten Loureiro, MPH	822-5366
MCC PRMC Chair and Regulatory Advisor: Carlos Carrera, MD	657-7085
MCC Data & Safety Monitoring Board (DSMB) Chair Fred Millard, MD	822-6185
MCC Quality Assurance Manager: Reza Faeldonea	822-5379
MCC CTO Internal Monitor: Roxana Phillips	822-5361
MCC CTO Senior Financial Analyst: Rita Trowbridge, JD	822-5398

Clinical Research Center: Melinda Richards	543-6180
Biosafety (Environmental, Health & Safety): Brenda Wong	534-6059
Molecular Pathology: Steven Gonias, MD, PhD	534-8955
Investigational Drug Pharmacy: James Gonzales, PharmD	543-2824
Biostatistics: Karen Messer, PhD	822-2054
Office of Contracts and Grants (PI Initiated Sponsored Research Agreements):	
Carroll Ekberg	534-9884
Research Compliance and Clinical Trials Administrative Services Office (CTAS)	
(Industry sponsored Clinical Trials Agreements):	
Gail Zydlewski	534-1021
Lisa Coscarelli, JD	822-3518
Angela Fornataro McMahill, JD	822-4650

## II. PROTOCOL PREPARATION GUIDELINES

In cancer research, a protocol is a written plan of a clinical experiment or study to be conducted with cancer patients or individuals at risk of cancer. A study is designed to evaluate new experimental therapeutic programs, translational research, and cancer prevention and control programs. Each protocol is designed to answer specific questions leading to the development of new and improved therapy for cancer patients.

### Therapeutic and Prevention Clinical Trial Phases

The development of a new therapy is carried out in phases:

*Phase I* - Phase I trials determine a safe dose for phase II trials and define dose-limiting and other acute effects on normal tissues. In addition, these trials may examine the drug's pharmacology and may reveal evidence of anti-tumor activity.

*Phase II* - The goal of phase II trials is to determine whether a new treatment has activity against particular cancers. The various tumor types are tested in phase II as distinct clinical entities, since each has different prognostic factors, eligibility requirements, and patterns of responsiveness to study treatments. These trials, therefore, serve as a screen for further study.

*Phase III* - Phase III trials usually compare a new treatment with a standard (or other experimental) treatment to determine clinically significant efficacy of the new treatment. Phase III trials often involve randomized assignment to treatment arms.

### Regulatory Issues

An organization (or individual) seeking to sponsor a clinical trial of an experimental drug or device must submit an Investigational New Drug or Investigational Device Exemption application (IND or IDE) to the Food Drug Administration (FDA). After submission of an IND or IDE, the FDA has 30 days to complete their review. An IND may also be required for clinical trials with commercially available drugs in a non-approved indication or program, depending on prevailing standards of care.

### Writing the Master Protocol (NCI format)

The following format for a protocol is consistent with federal requirements.

Elements of the protocol:

**Title Page** - This is the primary source of identifying information. A sample copy of a title page that provides identifying information and standard attachments is in **Appendix A**.



**Protocol Summary and Schema** - It is customary and helpful after the title page to have a one-page protocol summary that includes a list of eligibility criteria, a brief description of the treatment, and a diagrammatic schema of the timeline for on-study tests, randomization, treatment and response assessments. Important dose modification criteria for expected toxicities may also be listed.

**1.0 Objectives** - This is a clear statement of the goals of the study. The objectives help orient the protocol to represent a clearly thought-out research plan rather than merely a guide for clinical management. The study design should be capable of answering the questions posed by the objectives. Clearly stated primary and secondary objectives are necessary to ensure that the size of the study and the plans for patient management are adequate and unbiased with regard to the questions posed.

**2.0 Background And Rationale** - sufficient background information should be included so that the rationale for the study is clear. Any unpublished data relevant to the rationale should be included in this section. This section should review known toxicities encountered in previous Phase I and II trials with the study agent(s). In addition to the background and rationale included for therapeutic aspects of a study, information should be provided to support ancillary studies to be performed. The rationale should be clearly stated for studying particular correlations between tumor characteristic and outcome measurements (response to therapy, disease-free survival, overall survival, etc). The choice of the particular techniques to be used should also be justified.

**3.0 Patient Eligibility Criteria** - Studies with objective response as an endpoint should include clear statements specifying whether tumor sites to be followed for response must be measurable, what criteria must be fulfilled to consider disease measurable, whether evaluable disease is permitted, and, if so, at what sites. Also describe how subjects will be identified and recruited to the trial. The inclusion of women and minority groups must be addressed in developing a research design that is appropriate for the objectives of the study

**4.0 Pharmaceutical Information** - This section should include the product description (dosage forms, ingredients, packaging, supplier information), solution preparation instructions, storage requirements, stability, route of administration, and drug-associated toxicities. Information should be given for ALL investigational and non-investigational agents specified in the treatment plan.

**5.0 Treatment Plan** - Specify protocol treatment clearly so that it can be followed by all medical personnel.

**6.0 Study Entry Procedures** - Procedures for patient entry, whether randomized or non-randomized, should be specified. Required information includes the telephone number of the randomization desk or protocol registration office and the patient characteristics and stratification factors (if any) to be provided at the time of entry. Patients should generally be registered on study prior to beginning treatment.

**7.0 Dose Modification For Toxicity** - The plan of dose change for toxicity should be stated for each study drug. The conventional toxicity scale (e.g. NCI, CALGB, GOG) used for dose modification criteria should be specified and included as a protocol appendix. If this is an institutional study the NCI common toxicity scale should be used. Instructions for reporting adverse reactions should be included in the protocol text.

**8.0 Response Assessment** - The criteria for scoring responses should be included. These should be specific for both measurable and evaluable disease. Disease-specific criteria are often required and should clearly indicate acceptable means of measurement, e.g., CT scans, ultrasound, etc.

**9.0 Monitoring Of Patients** - Specify how patients will be followed for assessment of treatment toxicity and therapeutic effect. A table of follow-up parameters that incorporates the schedule as described is particularly useful.

**10.0 “Off-Study” Criteria** - Criteria for terminating protocol treatment and/or removing a patient from treatment or from study should be specified.

**11.0 Statistics** - An adequate statistical section discusses the study design in relation to the objectives of the study and the plan for the evaluation of the data, specifically, method of randomization; total sample size justified for adequate testing or primary and secondary hypotheses; error levels in phase III studies; differences to be detected for comparative studies; estimated accrual rate and/or study duration with supporting documentation, stopping rules, including statistical and administrative procedures for monitoring the progress of the trial to implement early termination; expected outcome parameters as appropriate; primary endpoint for interim and final analysis; clear specification of primary and secondary hypotheses; maximum number of patients; and plan for analysis.

**12.0 Record Keeping** - Specify the document on which each of the following is to be recorded, where it is to be sent, and on what schedule.

- On-study information, including patient eligibility data and patient history.
- Flow sheets, or other forms for interim monitoring.
- Specialty forms for pathology, radiation, or surgery when required.
- Off-study summary sheet, including a final assessment by the treating physician.

**13.0 References**- Source of information used in preparing the protocol.

**14.0 Multi-center Trials** - Identify the coordinating site and all participating institutions and local principal investigators. Verify that each participating institution has an assurance on file with the Office for Protection from Research Risks, NIH. Identify the protocol chair, who is responsible for assuring that IRB approval has been obtained at each participating site prior to patient entry from that site. The protocol chair is also responsible for the conduct of the study and monitoring of its progress, and will review all case report forms from participating investigators.

15.0 **Ancillary Studies** - Describe briefly the technical approaches to be used for ancillary studies. Describe plans for tissue procurement and banking. Discuss issues of sample anonymity or coding, access to samples by other investigators, and whether or not genetic research on inherited disease susceptibility markers is to be performed.

**All protocols must have the elements listed above or the protocol will be deferred.**

### **Protocol Attachments**

Investigators writing institutional therapeutic protocols may request copies of these attachments from the CTO Office.

- Eligibility Checklist Template
- Common Toxicity Criteria
- Adverse Event Report Form
- Case Report Form Template

#### *Note:*

It is the investigator's responsibility to ensure that the necessary collaborating and consulting arrangements have been made with Cancer Center investigators for the conduct of the proposed research. This is best done in the planning phase, particularly when access to specific patients is being sought. The CTO will guide investigators in making these arrangements as needed. Full statistical consultation through the Cancer Center's Biostatistics Facility shared resource unit prior to submission for IRB/PRMC review is strongly recommended for all Cancer Center protocols and each protocol document must contain a Statistical Considerations section.

### **IRB Application Procedure**

The application to the IRB is a succinct version of the master protocol, answering each of the 25 questions found in **Appendix B**. It should be sufficiently detailed to allow the reviewers to understand the important elements of the study independent of the master protocol. Copies of the master protocol along with the IRB application are submitted to the Human Subjects Program Office as well as to the PRMC office.

The Informed Consent is an important part of the IRB application. Each informed consent document must be protocol-specific and contain the elements required by Federal regulations. These regulations do not specify the language of the document but provide a list of elements that must be addressed in the text of the consent form. <http://ohsr.od.nih.gov/mpa/45cfr46.php3>. The consent should be written in lay terms and avoid medical jargon. Adequate definition of medical terms and descriptions of procedures are necessary.

Assistance with the consent may be obtained through the CTO. Guidelines are found in **Appendix C**.

## **GCRC Application Procedure**

If any part of the study will be conducted within the GCRC, an application to the GCRC is necessary. In addition to a copy of the IRB application, the GCRC application contains questions regarding utilization of the GCRC, tests, funding source, etc. See **Appendix D** for further information. The GCRC has a separate review committee for all applications with the same submission deadlines as the IRB application.

## **VA Participation**

By agreement, clinical trials at the La Jolla VA Hospital are reviewed by the University IRB; however, there is a variance in the application/approval process.

A VA responsible investigator must be identified. This is mandatory; the VA research office will not proceed without this.

A VA consent must be submitted to the University IRB for approval in addition to the UCSD consent if subjects will be recruited from both sources.

The VA Project Data sheet and Abstract form must be completed.

VA specific forms are in **Appendix E**.

## **Informed Consent**

Informed consent must follow strict procedures prescribed by the PHS, FDA and UCSD. Local information on informed consent requirements may be found at

<http://irb.ucsd.edu/consent.shtml>. Additionally, effective April 13, 2003 the Federal Health Insurance Portability and Accountability Act took effect. This law has important provisions on privacy of medical records and use of personal health information, which will affect the preparation of the consent form. More information on HIPAA may be found at <http://www.health.ucsd.edu/compliance/hipaa.shtml>.

### **III. CLINICAL TRIALS OFFICE**

The Moores UCSD Cancer Center is NCI designated and the Clinical Trials Office (CTO) is a Shared Resource of the Center intended to give practical help to peer-reviewed investigators wishing to conduct clinical studies. It should be one of the first resources contacted when an investigator is considering a new clinical trial at UCSD.

The CTO:

- Provides centralized administrative and management support for clinical trials
- Provides budget development and negotiation services
- Assists with trial design and implementation
- Promotes clinical trials, referrals, and subject recruitment
- Serves as an information resource for researchers, sponsors, referring physicians and patients
- Monitors all active and closed protocols

#### **Organization**

The Director of the Clinical Trials Office has overall responsibility for the policies and practices of the CTO, reviews quality control issues and any topics related to the functioning of the Shared Resource. The Director has a responsibility for assuring that all regulatory requirements as outlined by federal, state and institutional agencies/offices for experimental clinical trials are met. The Director reports to the Associate Director of Clinical Research and the Cancer Center Director.

The CTO Assistant Director has overall administrative responsibility for the CTO and reports to the CTO Director.

The CTO core Clinical Research Professionals (CRPs) are available for the coordination and management of institutional clinical trials. CRPs are responsible for the collection, coordination and compilation of data from the Cancer Center patient care areas as well as affiliated hospitals.

#### **Interactive Relationships**

The Clinical Trials Office is also an umbrella organization that organizes and coordinates the work of CRPs made available by grants from National Cooperative Groups (e.g. CALGB and NSABP) and agreements with drug companies for clinical trials approved by the Cancer Center. It is encouraged that CRPs supporting Cancer Center studies be administered and managed by the CTO, although it is realized that for some programs this is not logistically feasible. CRPs on Investigator-funded trials not managed by the CTO are included in the umbrella organization, attend monthly CRP meetings, and are subject to quality assurance and monitoring activities.

The Investigational Drug Service of the Pharmacy Department is responsible for management and control of investigational drugs used by CTO-supported programs. The Investigational Drug Services Pharmacist acts as a liaison between the Cancer Center physicians in charge of the study and the nurses and pharmacists working with the protocol.

## **Services Offered**

Services offered by the CTO include:

### *Administrative Support*

- IRB administration for institutional studies: to assist investigators with IRB forms, new and annual renewal submissions for institutional studies may be assembled and submitted by the CTO clinical research professionals based on currently available resources.
- Phone triage for physician/patient calls inquiring about clinical trials. Potential study subjects are referred to the appropriate CRP or PI.
- Protocols are displayed and kept current on the Cancer Center's website at <http://cancer.ucsd.edu/cto/index.asp>.

### *Centralization and Coordination of CRPs*

CRPs are housed within CTO offices located on the second floor of the MCC. Centralization of CRP activities enhances their efficiency. Weekly meetings of all CRPs, including investigator-funded CRPs not housed within the CTO, are held to address clinical trials issues, questions and problems, and for educational presentations by guest speakers.

Coordination of CRPs through the CTO facilitates information exchange, cross-coverage, reliability of access, training, and consistency of performance. Protocol audit/monitoring functions are coordinated by the Internal monitor.

### *Contract and Budget Assistance*

The Research Compliance and Clinical Trials Administrative Services Office (CTAS) provides clinical trial contracting services to protect investigator rights and interests as researchers and to ensure Sponsor terms are in compliance with University policies and procedures. When a physician is anxious to see the Protocol, the temptation is to sign the agreement. But BE AWARE if the physician signs the CDA as an individual, he/she is personally taking on the obligations and potential liabilities specified in the CDA. Should any of the obligations be breached, the Sponsor has the right to hold the physician personally liable. To protect the physician, the CDA should be reviewed by the Central Clinical Trials Office and signed by an authorized representative of the University. The University is then contracting on behalf of its employee, the physician, and will protect the physician should any issues arise. Forward all such requests from sponsors to Rita

Trowbridge, [rtrowbridge@ucsd.edu](mailto:rtrowbridge@ucsd.edu) (858) 822-5398, or the assigned CTO Project Manager for processing to CTAS office.

An adequate budget is imperative for the successful and smooth conduct of a clinical trial. Unanticipated and/or uncovered costs can severely impair a PI's success. To assist investigators, experienced personnel within the CTO are available to review proposed clinical study budgets, to ensure sufficient funds are available to run the trial. Investigators are encouraged to contact the CTO Senior Financial Analyst to arrange a budget review. Budgets must reflect reasonable estimates of all study costs including PI and collaborators effort, CRPs, regulatory review cost assessment, research drugs, tests, scans and assays, subject payment, if any, and indirect costs in conformance with University policy.

Assistance with applications for Clinical Trials Agreements or Sponsored Research Agreements can be obtained from the assigned CTO Project Manager.

#### *Clinical Trials Consultation Service*

Investigators who are considering a clinical study or are designing a trial should avail themselves of the services offered by Dr. T. Reid, and Dr. C. Carrera. Advice can be obtained regarding clinical trial design, IRB/PRMC/FDA regulatory requirements from Reza Faeldonea at (858) 822-5379, and practical issues such as subject availability, collaboration with other investigators with similar interests, etc. Investigators are strongly encouraged to make an appointment with Biostatistics Shared Resource for a trial design and biostatistical consultation.

#### *Clinical Research Environmental Data Information Tracking (CREDIT) System*

CREDIT is designed for protocol and patient data management. All patients enrolled onto study are registered with the CTO and entered into CREDIT, either directly by the CRP. Registration of all patients entered onto protocols is obligatory and is used to generate mandatory NCI Summaries 3 and 4.

#### *Subject Recruitment*

The CTO works to identify potential clinical trial participants prior to their clinic visit. Patients are screened by CRPs prior to their initial clinic visit to obtain general information in order to determine potential eligibility for a trial. This information and the relevant clinical trials are provided to the physician scheduled to see the patient.

The CTO assists as well with identification of potential collaborators, referrals to physicians who care for the relevant patient population and community physicians who may wish to interact on studies, and other means of patient recruitment such as community outreach.

## **Study Coordination**

Clinical Research Professionals (CRPs ) screen patients for eligibility. The CRPs or investigator is responsible for reviewing the study and consent form with patients, enrolling consenting patients and obtaining patients' signed consent form. A copy of the signed consent is forwarded to the CTO for its files.

The Clinical Research Professional for each study will register applicable patients with off-campus sponsors (e.g. CALGB, Drug Company, etc.) and assure the patient is also registered in the CTO patient database (CREDIT).

The Clinical Research Professionals (CRP) will monitor the treatment of patients and the collection of data as appropriate to complete Case Report Forms. The CRP will also schedule and coordinate external/internal audits with the CTO Internal Monitor to assure quality of data. Patient confidentiality will be maintained in accord with regulatory requirements.

A patient binder will be kept for each patient on study. The binders will include all source documentation for the case report forms. Diaries, logs, and updates will be recorded in the patient binder. A regulatory binder for each study, including all versions of the protocol, amendments, AE's, and IRB correspondence will be maintained by the CTO regulatory unit.

Per the Clinical Trial Agreement, the CRPs will follow patients off treatment, and continue to provide required data until study termination.

Outside physicians participating in a clinical trial must sign a written contract for the timely provision of data. All case report forms must be provided to the CTO on a monthly basis, with all trial data being subject to audit.

## **Patient Registration Procedures**

All new patients on Cancer Center clinical trials will be registered in the CTO patient registration database (CREDIT). Registration is accomplished by direct data entry.. Patient registration should be complete within 48 hours of the on-study date. Patient data are incorporated into a monthly patient accrual report, which is reviewed by the Principal Investigator and the CRPs.

The Clinical Trials Office is responsible for registering patients on the following protocols:

- a. Institutional Studies
- b. Cooperative Group Studies
- c. Industry sponsored Studies



## Quality Assurance

Timely, accurate and complete data are critical to the success of a clinical trial. This goal is normally achieved through an effective quality assurance (QA) program, which involves investigators, nurses, and clinical research professionals who are concerned with the administration of a study and the quality of data to support scientific conclusions.

All protocols are subject to quality assurance reviews by both external and internal QA monitors.

### *External Reviews*

It is the policy of the UCSD Medical Center to comply with all applicable healthcare laws and regulations and to cooperate with appropriately authorized governmental and/or other regulatory investigations and audits.

A variety of federal and state governmental and other regulatory agencies may be involved in healthcare-related investigations for various reasons. These agencies include, but are not limited to:

Office of Inspector General (“OIG”);  
Centers for Medicare and Medicaid Services (“CMMS” – formerly “HCFA”)  
Federal Bureau of Investigation (“FBI”);  
Department of Defense;  
United States Attorney’s Office;  
Medicare Intermediaries;  
California Attorney General’s Office;  
California Department of Health Services (Licensing and Certification Division, Medi-Cal Audit and Investigations Unit, et.al.);  
Joint Commission on Accreditation of Healthcare Organizations ([JCAHO](#))  
Food and Drug Administration (“FDA”).

When an agency investigator contacts an employee anywhere, such as at home or at the UCSD Medical Center, for information regarding the UCSD Medical Center or any UCSD Medical Center-affiliated health care entity, or any other entity with which the UCSD Medical Center does business, the employee should first contact their supervisor and then contact the Administrative Services Department immediately at (619) 543-5223 or (619) 543-3469. Employees are to be aware that, in initial inquiries regarding a matter to be investigated, the agency investigator may not disclose the fact that an investigation is underway.

It is very important that all principal investigators, CRPs and other appropriate staff should review complete instructions on external audits and notifications included in MCP 555.1 <http://www-ucsdhealthcare.ucsd.edu/MCPWeb/docs/555.1/doc.htm>. See Appendix G.

### *Internal Reviews*

All active institutional therapeutic protocols are subject to internal auditing.

The principal investigator (PI) should meet with the clinical research professional and define responsibilities. The Case Report Forms, consents, source documents, and regulatory binders should all be reviewed for completeness. The PI and CRP can meet with the manager of the CTO and review needed materials.

The first audit level verifies that the number of patients enrolled in CREDIT and the number of signed consent documents in the files are the same.

The next audit level monitors the timeliness of accrual and is carried out quarterly.

A level 3 or full audit includes informed consent, pre-therapy requirements, eligibility criteria, protocol compliance, dose modifications, toxicity and adverse event reporting, drug accountability, record keeping, quality of data and timeliness of data submission. At random, twenty percent or a minimum of five patients enrolled will be selected for in-depth review.

A subset of institutional protocols will be audited each year, with all institutional protocols subject to an audit at least once in a four-year period.

The manager of the CTO oversees the audit process and the monitor submits the findings to the Monitoring Subcommittee. For more details regarding monitoring and audits, see section IV, PRMC.

Investigators and the CRPs will be notified in advance of the level 3 full internal audit, which will be conducted in a fashion similar to the external audits. Similar compliance with auditing is expected. Studies that are externally audited are not subject to level 3 internal audits.

Effective June 2002 the Cancer Center also has an NCI approved Data Safety and Monitoring Plan that describes the criteria for a protocol to be subject to DSMB monitoring. A standing DSMB exists under the direction of Fred Millard, M.D.. For those studies subject to the Cancer Center DSMB, an annual DSMB level audit will also be conducted.

### **Adverse Events**

All adverse events are to be reported to the CTO as further described in the OHSP guidelines for adverse event reporting. Timely and accurate reporting of Adverse Drug Reactions (ADR) permits the sponsor to collate information from diverse sources and disseminate the results to investigators working with the drug. The centralization of this information makes possible a much more accurate determination of the degree to which

a suspected reaction is drug induced. Therefore, life-threatening or fatal and unexpected drug reactions will be submitted to the sponsor. Copies of written ADR's to the sponsor will be submitted to the IRB and PRMC (see the protocol for reporting timetable and specific instruction); see Appendix D for additional guidelines and report forms.

## **Data Management**

Data management for protocols is the responsibility of the Principal Investigator, but may be coordinated by the Cancer Center Clinical Trials Office.

## **Policies**

The full range of CTO services and programs are available to all Cancer Center members with an interest in clinical or translational cancer research. Resources are not available for non-members of the Cancer Center, or for proposals that are rejected or deferred by the PRMC. Cancer Center member trials will be kept in the protocol library and included in the protocol booklets.

Registration with the CTO and entry into CREDIT of all patients entered onto protocols is obligatory. A copy of the signed consent must also be sent to the CTO for its files as a part of the monitoring function.

Centralization of CRPs within the CTO is strongly advised. All CRPs will attend the regularly scheduled CRP meetings and educational sessions.

Investigators requiring the services of a CRP will contact the CTO to discuss their needs. For large programs, a dedicated CRP will be identified. Otherwise, a percentage of a core CRP's time may be arranged. The investigator's research budget will be charged for the CRP's time.

Allocation of CRP resources is the responsibility of the CTO Director, who will review their workload together with the CTO Project managers..

The Director of the CTO reports to the Deputy Director of Clinical Oncology who reports to the Cancer Center Director.

CRP support for unfunded studies, such as pilot or feasibility studies, will be arranged based on the merit of the project. The CTO Director, together with the Cancer Center Director and Associate Director of Clinical Research will determine the level of support after review of such requests.

## **IV. PROTOCOL REVIEW AND MONITORING COMMITTEE (PRMC)**

### **Goals and Responsibilities**

The PRMC is a multidisciplinary standing committee of the Moores UCSD Cancer Center, established to facilitate the conduct of scientifically meritorious clinical research by Cancer Center investigators.

The PRMC has dual primary responsibilities:

- (1) Perform scientific peer review of cancer-related clinical trials involving cancer patients prior to evaluation by the Institutional Review Board (IRB) of the UCSD School of Medicine,
- (2) Review the scientific progress and accrual of active Cancer Center clinical protocols through a periodic monitoring and in-depth auditing process.

### **Authority and Relationship to the IRB**

The PRMC is granted the authority by the Cancer Center Director to:

- (1) approve cancer-related research protocols for activation at the University;
- (2) issue binding recommendations for protocol modification or amendment for reasons of scientific validity or medical value;
- (3) defer activation of protocols with deficiencies in content, study design, or feasibility; and
- (4) close protocols due to changes in scientific knowledge, or if monitoring data reveals unjustifiably low accrual rates or unacceptable risk to participating subjects.

The function of the PRMC is complementary to that of the IRB. The PRMC and UCSD School of Medicine Human Subjects Committee conduct protocol review procedures for cancer-related research in tandem. Two members of the PRMC serve as Cancer Center representatives on the Human Subjects Committee, establishing continuity between the review procedures of both committees.

Findings of the PRMC review process become an integral part of the IRB review of cancer-related clinical protocols. PRMC recommendations for modification or clarification of specific study design issues are transmitted to investigators as part of the Human Subjects Committee notice of action. For conditionally approved protocols, the investigator's reply and required modifications are reviewed for accuracy and completeness by the PRMC/IRB Cancer Center reviewer, prior to final protocol approval and activation. Protocols deferred following PRMC review cannot be approved for activation by the UCSD Human Subjects Committee, and must be resubmitted for full committee review by both the PRMC and the IRB.

## **PRMC Composition**

### *Leadership*

The PRMC Chair is appointed by the Cancer Center Director, and a Vice Chair is appointed by the PRMC Chair. Both Chair and Vice Chair serve as Cancer Center representative members of the UCSD IRB. The PRMC Chair reports on activities of the committee to the Cancer Center Director, and also serves as a Regulatory Advisor for investigators seeking specific information on FDA and IRB regulatory issues and requirements.

### *Membership*

The PRMC is multi-disciplinary and includes representatives of the following specialties:

- Medical Oncology
- Surgical Oncology (or surgical oncology sub-specialty)
- Pediatric Oncology
- Radiation Oncology
- Biostatistics
- Oncology Clinical Nurse Specialist
- Investigational Drug Pharmacist
- CTO Manager

Ad hoc members called in when protocols require their expertise:

- Cancer Prevention & Control
- Gynecologic Oncology
- Community Outreach
- Immunology
- Gene Therapy

Ex officio members:

- Director, UCSD Cancer Center
- Associate Director of Clinical Research
- Associate Director of Basic Research
- Associate Director for Administration

## **PRMC Review Process**

### *Meeting Schedule*

PRMC meetings occur routinely two days prior to the regularly scheduled semi-monthly meeting of the School of Medicine Human Subjects Committee. Application submission deadlines are the same for both committees.

### *Application*

Protocol application formats include (a) a detailed master protocol from an NCI cooperative group, from a corporate sponsor, or one prepared by the investigator in the format recommended in the NCI Investigator's Handbook, and (b) the standard IRB application complete with informed consent document.

### *Classification of Protocols*

Cancer-related clinical protocols reviewed by the PRMC include those developed by UCSD faculty investigators, by National Cancer Cooperative Groups (i.e., CALGB, RTOG, POG) and CTEP, and by pharmaceutical or medical device industry sponsors. Submitted protocols undergo PRMC review at one of three levels:

- (1) Clinical or translational research protocols initiated by UCSD faculty members (institutional protocols), or protocols initiated by faculty at other academic institutions seeking collaboration with UCSD (collaborative institutional protocols), are subject to detailed scientific, biostatistical, and feasibility review.
- (2) Multi-center trials initiated by corporate sponsors are reviewed for scientific rationale, study design, and validity of the data analysis plan.
- (3) National cooperative group protocols are subject to informational review. Progress reports are assessed for national and local accrual rate and for the impact of toxicity profiles on risk management procedures.

### *Reviewer Assignment*

Applications are assigned to primary and secondary reviewers, neither of whom is an investigator on the protocol. In addition, the PRMC biostatistician reviews all applications. Each reviewer completes a Protocol Evaluation Form (*Appendix G*).

When necessary, an ad hoc member with particular expertise and interest will be assigned as the primary reviewer.

## Review Parameters

Institutional and collaborative institutional protocols are reviewed according to these criteria:

- (1) **Scientific Rationale:** There must be a clearly enunciated hypothesis, which is being tested. This hypothesis must take into account an adequate analysis of published data. Primary and secondary specific aims must be explicitly stated. The completed study should hold real promise of producing generalizable and useful new knowledge.
- (2) **Study Design and Biostatistical Merit:** The statistical considerations (including method of analysis, stopping rule, and/or sample size calculation) must be clearly linked to the stated objectives or specific aims of the research. For therapeutic research, specific statistical information is required depending on the kind of clinical trial proposed:

*Phase I studies:* A rule for the dose escalation and stopping rule must be specified. If a fixed sample size is to be used, a sample size calculation must justify the sample size chosen. Dose Limiting Toxicity (DLT) and maximum tolerated dose (MTD) must be defined.

*Phase II studies:* The number of patients to accrue must be justified by a reasonable sample size calculation or stopping rule. An explicit description of the calculation or rule (including  $\alpha$  and  $\beta$  errors and assumptions about response rates) must be given.

*Phase III studies:* The number of patients to accrue must be justified by a sample size calculation and/or stopping rule. An explicit description of the calculation or rule (including  $\alpha$  and  $\beta$  errors and assumptions about response rates or other outcomes) must be given. The method of analysis of the primary endpoints, including plans for interim analysis of the data, must be specified. The method of randomization needs to be described; if stratification is to be performed, the strata must be defined, and whether the analysis will be carried out separately for each stratum or for all strata combined.

Guidelines for statistical data analysis and sample size calculation or stopping rule for *non-treatment studies* (e.g., marker studies) are generally similar to those for Phase II/III studies. If risk in excess of that associated with a venepuncture, bone marrow biopsy or leukapheresis are anticipated, a sample size calculation and/or stopping rule must be given. If interim analyses are to be performed, the details of these must be spelled out.

*Pilot or feasibility studies* must have statistical considerations that parallel quantifiable objectives. If the purpose of the pilot study is to decide whether to

proceed with a larger study, then a rule for deciding to proceed beyond the pilot stage must be stated.

- (3) **Expected Accrual:** An estimate is required of the expected accrual duration of the study and the data source used to calculate the estimate. Competing protocols at UCSD must be identified with the assistance of the CTO database, and an explanation is then required of how patient accrual will be affected by competing studies. Documentation may be required if accrual depends upon collaboration of other physicians or groups. Two years is a typical period for patient accrual to be completed. Ordinarily, four years is the maximum.
- (4) **Safety of Proposed Research:** The potential for benefit to the individual subject, or to society from knowledge gained, must justify the risks of participation. Appropriate risk monitoring and modifications procedures must be specified and adverse event reporting procedures must be described. Notwithstanding any decision of the PRMC regarding safety or ethical issues of subject participation, the criteria and decisions of the IRB will take precedence.
- (5) **Feasibility:** The protocol descriptions of research and nursing personnel effort, utilization of facilities, and support for biostatistics consultation, research laboratory tests and ancillary costs are assessed for feasibility of the study.

**PRMC Actions and Decisions**

A majority vote by members present or their designees determines the decision taken.

PRMC Decisions and Actions	
Approved	Decision forwarded to IRB
Approved pending FDA action on pending IND	Decision forwarded to IRB
Approved pending modification, amendment, protocol clarification	Decision and comments forwarded to IRB
Deferred	Decision and comments forwarded to IRB

**Outcome of PRMC Actions**

PRMC review comments and requests for protocol modification or clarification are integrated into the IRB review by the PRMC representative member of the Human Subjects Committee. Investigator responses to comments concerning substantive issues of scientific rationale, study design, biostatistics, or risk modification procedures are reviewed by the PRMC/IRB Cancer Center Member prior to protocol approval and activation by the IRB. Protocols deferred by either committee must be resubmitted with appropriate modification or amendment to both the PRMC and the IRB for full committee reviews.



## Record Keeping

Actions taken on each protocol and comments to the investigator are recorded in the minutes of the meeting. The minutes are distributed to the IRB. The protocol evaluation forms completed by primary and secondary PRMC reviewers and by the PRMC biostatistician are attached to the meeting minutes and filed in the Protocol Review and Monitoring Office.

## Protocol Monitoring

All active institutional protocols are subject to continued monitoring by the Protocol Review and Monitoring Committee. Patients are registered in the patient registration database of the Clinical Trial Office (CTO). Three levels of monitoring are carried out.

*Level 1:* Documentation of informed consent:

The number of consent form documents submitted to the CTO should correspond to the number of patients enrolled.

*Level 2:* Documentation of subject accrual:

Monitoring is carried out every three months. Guidelines for accrual monitoring are:

*First Anniversary:* If 0-3 patients are accrued, the accrual may be considered insufficient. A satisfactory response and plan to increase accrual is required from the investigator to prevent closure.

*Second Anniversary:* If less than 50% of projected accrual has been achieved, the feasibility of attaining the accrual goal may be in question. A response is required from the investigator.

If more than 100% of projected accrual has been achieved, the study will be considered for closure. A response is required from the investigator justifying continued accrual.

*Fourth Anniversary:* Most institutional studies are considered feasible only if they can be completed in four years. If less than 100% of projected accrual has been achieved, then the accrual is considered potentially insufficient. The study will be considered for closure. A response is required from the investigator justifying extension for an additional year. If accrual is less than 75% of projected, closure of the study is likely.

If 100% or more of projected accrual has been achieved, the study will be considered for closure. A response is required from the investigator justifying continued accrual.

The above information is forwarded to the PRMC. Recommendation for closure will be made by the PRMC and filed with the CTO. The IRB is notified of all closures.

*Level 3: In-depth protocol audit:*

A clinical research professional from the CTO will conduct in-depth annual audits of institutional clinical trials. The audit will include informed consent, pre-therapy requirements, eligibility criteria, protocol compliance, dose modifications, toxicity and adverse event reporting, drug accountability, record keeping, quality of data and timeliness of data submission. At least 25% of the subject records will be audited.

Protocols become subject to Level 3 audit after the First Anniversary of study activation. Approximately 25% of all institutional protocols will be audited each year.

### **Protocol Closure and Termination**

Upon review of monitoring data or audit reports, the PRMC may recommend termination of clinical research protocols for any of the following circumstances:

- (1) Insufficient subject accrual to accomplish the study aims.
- (2) There is no longer a requirement to accrue new subjects. However, if there is a subject follow-up requirement, data will continue to be collected and a progress report must be submitted to the IRB and CTO at least once a year.
- (3) There is no requirement for subject follow-up because all patients have expired.
- (4) Target accrual or specific aims of the protocol have been accomplished.
- (5) New scientific findings obviated the need to continue the research.
- (6) Conduct of the research is of such poor quality as to make the findings of the protocol questionable.
- (7) The frequency or severity of adverse events puts subjects at undue risk, or other ethical concerns are raised.

PRMC members who are present vote to recommend termination of the protocol and the investigator and IRB are notified. The PRMC recommendation is ordinarily considered binding, and any response or rebuttal from the investigator together with the PRMC report is then filed with the Cancer Center Director. The investigator may appeal the PRMC action to the Center Director; the decision of the Director is final.

## **Prioritization of Clinical Protocols**

The appropriate specialized cancer unit leader will assign approved clinical and translational research protocols a priority classification (top, high, or low). The PRMC office will receive an updated list of prioritized protocols from these cancer units on a quarterly basis. Questions from investigators regarding a priority assignment may be submitted to the PRMC for consideration as a meeting agenda item, and the resulting commentary and recommendations will be recorded in the PRMC minutes and reported to the specialized cancer unit leader and to the Cancer Center Director.

Protocols for which an appropriate specialized cancer unit does not yet exist will be assigned a priority classification at the time of PRMC approval. Priority classifications are generally assigned as follows (descending order):

- (1) Investigator-initiated, externally funded protocols
- (2) Investigator-initiated, internally peer-reviewed protocols
- (3) National cooperative group or CTEP-sponsored clinical trials
- (4) Industry-sponsored clinical protocols