

**University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center**

PRMS Protocol Review Committee (PRC) Review Policy

PRMS Procedure for Protocol
Review by PRC

Purpose

Per CCSG Guidelines, it is particularly important for Centers involved in clinical research to establish a mechanism for assuring adequate internal oversight of the conduct of all cancer clinical trials in the institution or institutions that formally comprise the Center. The focus of the Protocol Review and Monitoring System (PRMS) is on *scientific merit, priorities and progress* of the clinical research in the Center. The PRMS should have the authority to open protocols that meet the scientific merit and scientific priorities of the center and to close protocols that do not demonstrate adequate scientific progress.

PRMS responsibilities at this institution are carried out on two separate levels to ensure optimal oversight of progress and performance. There is initial review by the applicable Program Site Committee(s), followed by independent review by the Protocol Review Committee (PRC). The purpose of this policy is to document the full review processes undertaken by the Protocol Review Committee.

Procedures

Meeting Schedule

The Protocol Review Committee meets monthly; if there is sufficient demand, additional meetings are called.

Review Functions

One central Protocol Review Committee evaluates all clinical trials involving patients with cancer or those at risk for cancer undertaken at the University of California San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center (hereafter referred to as the HDFCCC) and its affiliates.

The committee is required to:

- Review all documents submitted in applications, including protocols, consent forms, site committee review forms and review outcome forms, pertinent protocol information, and, as applicable, investigator's brochures, surveys, quality of life questionnaires, other tools, and letters of support (protocols must meet the minimum set of guidelines and standards included in the HDFCCC

protocol template; see template or the ICH GCPs Section 6, <http://www.ich.org/LOB/media/MEDIA482.pdf>)

- Assess targeted annual accrual expectations, justification for accrual goals or prior accrual for similar population, and competing trials for each new clinical protocol
- Review and assess the review forms and Final Overall Score submitted by the Program Site Committees for all new protocols
- Undertake scientific review (evaluate the scientific questions, the validity of the study design and the biostatistical methods employed in all studies) of all submitted protocols and subsequently assign an Overall Scientific Score to all new protocols
- Ensure that all new protocols have appropriate data safety monitoring plans in place
- Determine whether a Data Safety Monitoring Board (DSMB) is required; and working with the DSMC to ensure a study-specific DSMB is formed, if applicable
- Ensure that all review concerns are adequately addressed and the protocol is appropriately revised prior to issuing Approval
- Review and approve all protocol amendments per HDFCCC standards (see **PRMS Amendment Review Policy**)
- Maintain written records of all meetings
- Assess accrual and scientific relevance for all open and enrolling studies which are not PRC exempt.
- Request (and approve) corrective action plans for poorly accruing studies, and close studies that do not meet accrual standards per HDFCCC criteria.

New Protocol Review Types

All clinical trials studying patients with cancer or those at risk for cancer conducted at the HDFCCC and its affiliates require PRC review. Review is either by the full committee or by the Chair or Vice Chair (expedited). All new submissions are triaged by the PRC Administrator and processed accordingly. Trials exempt from review by the PRC are also triaged by the PRC Administrator. All PRC submissions and reviews are managed electronically in a secure electronic web-based database. Review and exemption parameters are defined below.

Studies requiring full committee review:

- *Institutional (investigator-initiated)* interventional clinical trials involving human subjects that are developed by a UCSF investigator and are prospective studies involving human subjects designed to answer specific questions about the effects or impact of particular biomedical interventions such as drugs, treatments, or devices. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for cancer. Investigator-initiated research which may be multi-center and for which UCSF may or may not be the core or originating institution (coordinating center) will be considered as an investigator-initiated clinical trial. While the grant that funds an investigator-initiated trial may have been peer-reviewed at the national level, HDFCCC PRC review of the trial is also required.
- *Institutional* interventional behavioral or psychosocial clinical trials developed by a UCSF investigator that are prospective studies involving human subjects designed to answer specific questions about the effects or impact of particular behavioral interventions, including interventions whose goals are to increase behaviors (e.g. cancer screening, physical activity, fruit and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life (e.g., among cancer survivors) and reduce the negative sequelae of treatment. Interventions may pertain to cancer prevention, early detection, and survivorship. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for cancer. Investigator-initiated research which may be multi-center and for which UCSF is the core or originating institution (coordinating center) will be considered as an investigator-initiated clinical trial. While the grant that funds an investigator-initiated trial may have been peer-reviewed at the national level, HDFCCC PRC review of the trial is also required.
- *Institutional* prospective molecular or imaging diagnostic clinical trials that use the information from the diagnostic test in a manner that affects medical decision-making for the study subject.
- *Non NCI-cooperative group consortium studies* are reviewed as if investigator-initiated and must meet the above institutional criteria to receive full committee review.
- *Industry (commercially-sponsored)* clinical trials are commercially funded prospective studies involving human subjects designed to answer specific questions about the effects or impact of particular biomedical interventions such as drugs, treatments, or devices. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for cancer. Commercially-sponsored clinical trials must have a formal arrangement for audit of the data in order to be included in this category; trials that do not have data audit will be considered under the institutional category.
- *Standard of Care* studies that are prospective, non-randomized single arm treatments for a particular disease, where the treatment regimen is NOT the subject of the research. The regimen should be considered reasonable and

appropriate therapy for the disease, and the protocol should justify the “standard of care” status of the treatment. Outcome measures may include survival, disease-free survival, major toxicity, quality of life, or other administration-related quality endpoints. The goal of a standard of care study is to administer therapy in a uniform way and to track measures of quality of care and outcome.

Studies requiring expedited review:

- All *cooperative group trials* involving human subjects that are sponsored by a national clinical trials organization with NCI approval and external funding mechanisms, regardless of whether or not they involve interventions. These trials are externally peer-reviewed and are audited on a schedule determined by each cooperative group.
- Prospective *Institutional or Industry* molecular or genetic epidemiology studies and other research studies that evaluate aspects of cancer patient care including quality of life and may impose some risk on study subjects, but do not answer specific questions about the effects or impact of particular biomedical interventions and do not use the information from the diagnostic test in a manner that affects medical decision-making for the study subject.
- Other external peer review studies also qualify if they were previously peer-reviewed by the various NIH mechanisms (e.g., R0ls, U0ls, U10s, P0ls, and P50s), other approved agencies meeting the NIH standard, and clinical research protocols approved by the NCI’s Cancer Therapy Evaluation Program or the Cancer Control Protocol Review Committee.

Studies exempt from review:

- *Institutional* chart review studies, i.e., retrospective research within individual institutions, such as patient care evaluations performed for Commission on Cancer approval. Data from multiple institutions may be pooled within the limitations of the regulations governing risk management within each institution. Registry-based studies are included in this category.
- *Institutional* registries, databases, and serum and tissue banks created by members of the HDFCCC, regardless of their location, as long as the primary information about the patient is collected by members of the HDFCCC and the information which relates to patient identity is maintained at the HDFCCC.
- Molecular or genetic epidemiology studies and other research studies that evaluate aspects of cancer patient care including quality of life but do not involve cancer patients, do not answer specific questions about the effects or impact of particular biomedical interventions and do not use the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject.
- Diagnostic studies that do not impose any risks on subjects and do not use information from the diagnostic test in any manner that can affect the outcome of

study subjects, but whose objective is only the gathering of data on the characteristics of a new diagnostic approach.

- *Institutional* observational studies and others (e.g., quality of life, questionnaire) that do not test interventions.

New Protocols -- Full Committee Review

The PRC Administrator reviews new protocol submissions for completeness, assigns to a statistician not involved in the study development and design (the name of the statistician involved in study design found on the PRC application and the programmatic affiliations of PRC biostatisticians found on <http://cancer.ucsf.edu/cores/biostatistics-contacts> are cross-checked), and places each application on the next available agenda. Once placed on an agenda, the PRC Chair or Vice Chair assigns individual reviewers to each protocol (one primary and at least one secondary reviewer). Following notification, but prior to the meeting, committee members complete a full committee review form online using the secure electronic web-based database after reviewing the entire submission (consisting of a protocol, consent form[s], site committee review forms and review outcome forms, PRC application information, and, as applicable, investigator's brochure[s], surveys, quality of life questionnaires, other tools, and letters of support).

The full committee review form consists of a combination of check-boxes and fill-in-the-blank questions to ensure that all required concerns are discussed consistently by all reviewers. There are separate questions for primary reviewers, secondary reviewers, and statistical reviewers, which encompass the following issues:

- General and Feasibility Review: Are the investigators appropriate, are competing protocols prioritized*, how is bias avoided in enrollment when there are competing trials*, identify potential conflicts, funding source appropriate, does the science justify the risks?
- Accrual Goals: Are accrual goals realistic, and are they likely to be met?
- Study Objectives: Are objectives scientifically sound and accurately reflected in the consent form?
- Study Design: Can the study meet the objectives and answer the statistical question?
- Statistical Design: Is the statistical design appropriate, endpoints adequate, and the sample size calculation/power sufficient?
- Data Safety Monitoring: Is DSMC or DSMB necessary and included, and are stopping rules necessary, included, and satisfactory?
- Analysis Plan: Are planned analyses appropriate?
- Children, Women and Minorities: Is a plan for each group necessary and included?
- Final Scientific Score: Does the reviewer agree with the Program Site Committee score, and what is the reviewer's recommendation for Final Scientific Scores for the protocol?
- Review Outcome: List concerns requiring response and review outcome recommendation (Approved, Contingent Approval, or Disapproved).

* Protocol Prioritization: Two prioritization lists are required for each protocol: 1. Overall protocol development priority for the site committee; 2. Prioritization of competing

protocols open or planned for same patient population. Thus each Program Site Committee is required to numerically rank each submitted protocol in relation to all other trials under development from that Program Site Committee. Second, trials competing for the same patient population are identified in the PRC application information, and how enrollment to such trials will be ordered is described. The PRC evaluates both sets of information to determine how bias in enrollment will be avoided, and to assess trial feasibility.

Feasibility: PRC will not review a new protocol unless the projected accrual meets the accrual projection requirements in the table below:

Type of Trial	At least 5 patients accrued / year required?	Complete total target accrual in 3 years?	Orphan disease accrual criteria (IF waiver granted)
(UCSF) Investigator Initiated, Single Center	Yes*	Yes*	≥ 3 patients accrued per year, AND accrual completion within 5 years
(UCSF) Investigator Initiated, Multi-Center	Yes*	Yes*	≥ 1 patient per year accrued @ UCSF, or ≥ 3 patients per year accrued nationally, AND accrual completion within 5 years
Non-UCSF Investigator Initiated, Consortium or Coop group (UCSF not lead)	Yes*	No	≥ 1 patient per year accrued @ UCSF
Industry	Yes	No	N/A

*Waiver requests are allowed for these studies. Requests for waivers are submitted electronically and must justify why it is necessary to open such a low accruing study. Industry trials will not be granted waivers. Waivers to these requirements can be granted on a case by case basis by the PRC Chair, provided one of the following two criteria are met:

1. Unique correlative science will be undertaken by a UCSF investigator that will be informative even with a small number of UCSF accruals.
2. The disease being studied represents an “Orphan” disease, consisting of a malignancy with an annual incidence in the U.S.A. of <10,000 new cases.

No other justifications will be approved by the PRC. If the request for waiver is approved the protocol undergoes standard formal PRC review. If the request for waiver is declined the study is returned to the submitter without formal review. The PRC Administrator checks for accrual criteria and for waiver requests, and ensures PRC Chair review of waiver requests. Any new protocols not meeting the minimum accrual

criteria in the above table which do not have approved waiver requests in place will not be processed for formal PRC review.

Each reviewer considers the Program Site Committee review forms and summary of review form, and all other submitted documents including the protocol and all pertinent protocol information. Each reviewer then completes the PRC full committee review form as above, which includes scoring using the NIH scale. Each reviewer scores across a variety of domains (objectives, trial design, innovation/science, statistics, DSMP competing trials, and accrual/feasibility) and recommends a Final Scientific Score (not an average) for each trial.

A quorum is required for the conduct of every PRC meeting. Quorum is defined as greater than or equal to 50% of the Core Membership. Principal Investigators (PIs) and those otherwise involved in the study design are not allowed to be present for committee discussions. Prior to review of each protocol, any members who are in any way involved in the study design are asked to leave the room. At the meeting the primary reviewer presents the study to the members, and all assigned reviewers give their own assessments. The discussion is then opened up to all members present. Following discussion, the PRC Chair or Vice Chair summarizes the committee's concerns and the final review outcome, and the PRC committee determines the Overall Scientific Score for each trial by averaging the votes for Final Scientific Score by all members present. Reviewers' scores for each protocol will be averaged with the scores from all voting members present to determine the Final Scientific Score. Potential review outcomes are:

1. Approved
2. Contingent Approval (not ready for forward movement; the concerns are such that the response need only be reviewed by the original reviewers)
3. Disapproved (not ready for forward movement; the concerns are such that the response needs to be discussed by the full committee)

Following the meeting members are asked to finalize their full committee review forms in the secure electronic web-based database. Once all are finalized, the PRC Administrator drafts the minutes in the secure electronic web-based database, and the PRC Chair or Vice Chair reviews, edits, and signs off. Once the PRC Chair or Vice Chair signs off on the minutes, a review outcome memo is created. Once the protocol is approved, a review outcome memo indicating approval is created and sent to the study PI. Approval notifications and review outcome memos will include the committee's Overall Scientific Score.

Protocol Disposition Based on Review Outcome

1. Approved

If the protocol is approved, no further action is necessary until the protocol is amended. Requires a Final Scientific Score of 3 or less.

2. Contingent Approval

Contingent Approval memos will contain a discussion of what concerns need to be addressed before approval is granted. Such memos enumerate each concern and require the PI or designee to respond to each concern point by point. Requires a Final Scientific Score of between 4 and 6. Responses are filed in the secure electronic web-based database by either the PI or designee.

Responses to a Contingent Approval go back to the original reviewers. The PRC Administrator reviews the response for completeness and relays the response to all original reviewers. If an original reviewer is unavailable, a replacement reviewer is assigned by the Chair or Vice Chair. Each relevant reviewer completes a contingent response review form in the secure electronic web-based database to document the review. Reviewers are responsible for ensuring that all concerns are adequately addressed, that the protocol is revised appropriately, and that it is given a new score.

If one or more of the relevant reviewers recommends Contingent Approval or Disapproved, then that automatically becomes the next review outcome. If the protocol receives a second Contingent Approval the PI will be asked to respond a second time, but the PI's second response goes to the PRC Chair or Vice Chair for adjudication instead of going back to the original reviewers.

3. Disapproved Studies

Disapproved memos will contain a discussion of what concerns need to be addressed before approval is granted. Such memos enumerate each concern and require the PI or designee to respond to each concern point by point. Requires a Final Scientific Score of 7 or greater. Responses are filed in the secure electronic web-based database by either the PI or designee.

Responses to a Disapproval are re-assigned to the original reviewers whenever possible and placed on the next available agenda. They go before the full committee and are evaluated in the same manner as new protocols, with the same possible outcomes: Approved, Contingent Approved, Disapproved. The PRC Administrator reviews the response for completeness and relays the response to all original reviewers. If an original reviewer is unavailable, a replacement reviewer is assigned by the Chair or Vice Chair. Each relevant reviewer completes a full committee review form in the secure electronic web-based database to document the review. Reviewers are responsible for ensuring that all concerns are adequately addressed and that the protocol is revised appropriately. These forms are included in the deliberation of the committee.

The PRC will not approve any therapeutic phase III trials without a Data Safety Monitoring Board (DSMB). If the PRC determines that a DSMB is required on an investigator-initiated protocol, the PRC will request that the PI convene a study-specific DSMB and will notify the Data Safety Monitoring Committee (DSMC) of this request. The DSMC will work with the investigator to draft a charter and advise regarding potential Board membership. Details on what types of trials require DSMBs and how they are convened are found in the HDFCCC Policy and Procedures for Data Safety Monitoring.

New Protocols -- Expedited Review

Expedited studies are submitted and reviewed for completeness by the PRC Administrator. Submissions should include all Program Site Committee review forms and the review outcome form; at minimum they must include a numerical ranking of the submitted protocol in relation to all other trials in development from the relevant Program Site Committee, and the competing protocols identified in the PRC application information. The PRC Administrator then assigns the study to the PRC Chair or Vice Chair for review, which normally occurs within two weeks of submission. The Chair/Vice Chair assesses prioritization, conflicts with current protocols, adequate resources,

accrual, and local recruitment and patient protection issues. The accrual and waiver criteria in the table on page 6 apply to expedited reviews. Review is documented on the expedited review form, and approval or a review outcome memo is issued. If not approved outright, a Contingent Approval is given; this occasionally results in the Chair/Vice Chair referring the protocol to full committee, in which case the protocol is reviewed as in New Protocols -- Full Committee Review above. Contingent Approval notifications will contain a discussion of what concerns need to be addressed before approval is granted.

Expedited Review of Responses to Contingent Approval

After receipt of an expedited Contingent Approval response, the PRC Administrator reviews it for completeness and relays the response to the PRC Chair or Vice Chair. The PRC Chair or Vice Chair reviews the response and documents that all concerns are adequately responded to and that the protocol is revised appropriately. If the concerns are met appropriately, the protocol is given approval.

Protocol Amendment Review

Once a protocol is approved by the PRC, all future changes to that protocol are termed amendments and must be reviewed by the PRC. Amendment submissions are standardized per the PRMS Amendment Submission Policy. See PRMS Amendment Review Policy for review procedure.

Protocols exempt from PRC review do not require amendment review by the PRC.

Protocol Withdrawals

Principal Investigators (PIs) of new protocols not approved by the full committee are given three months in which to respond (from the time of notification of review outcome). If no response is received after three months, reminder correspondence goes out to the PI informing them that the protocol will be withdrawn in another three months if they do not respond. New unapproved protocols without a response six months from the time of original notification of review outcome will be automatically withdrawn by the PRC. If PIs wish to reactivate protocols following withdrawal, they must begin the protocol application process anew. PIs can withdraw protocols themselves at any time; they are asked to supply the reason for withdrawal.

Progress and Performance Monitoring

All enrolling studies are monitored annually for scientific progress and accrual objectives, both by the Program Site Committees and the PRC. Program Site Committees perform annual review to ensure adequate accrual to clinical trials, to close trials with poor accrual, and to ensure appropriate utilization of resources at the disease-specific level. Program Site Committees are required to either close poorly accruing studies or develop corrective action plans. Program Site Committee procedures are described under the PRMS Program Site Committee Review Policy.

The PRC independently monitors all enrolling studies for scientific progress and accrual objectives and has the authority to request corrective action plans or to close studies that are poorly accruing or for which the scientific relevance has changed.

While the Program Site Committees are expected to assume responsibility for accrual monitoring and closure of poorly accruing studies, the PRC has final authority regarding closure of non-accruing studies. I.e., protocols allowed to continue enrollment by the relevant Program Site Committee are not exempt from annual progress and performance monitoring and closure by the PRC. See PRMS Protocol Closure Policy for PRC review procedures for scientific progress and accrual objectives, as well as closure procedure.

DSMC Monitoring Reports

The DSMC will forward any monitoring reports with an outcome of “Significant Findings” or “Unsatisfactory” to the PRC for review. The PRC will utilize these reports in its progress and performance monitoring and evaluation of trials.

Alternate Procedure

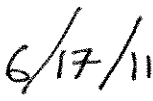
None.

Policy Approval

This policy document was approved by the following personnel on the following dates:



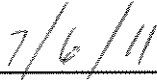
Eric Small, MD
Director, Investigational Trials Resource



Date



Judith Luce, MD
Chair, Protocol Review Committee



Date