

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

PRMS Program Site Committee Review Policy

PRMS Procedure for Protocol Review by
Site Committee

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 review process undergone by the programmatic Site Committees prior to review by the Protocol Review Committee.

Procedures

Meeting Schedule

All Program Site Committees are required to meet monthly at minimum. Larger groups may meet more than once per month if workload dictates. Phase I or otherwise high-risk/early phase clinical trials must be reviewed at weekly meetings.

Review Functions

Program Site Committees will be formed for each CCSG-funded program, and may be formed for non-CCSG-funded programs as well. There are also Program Site Committees established for early phase studies, other cancers (for research programs too small to meet the minimum membership requirements), and symptom management/palliative care/survivorship interventional trials crossing many cancer sites. Research programs large enough to meet the minimum membership requirements may still choose to join the site committee for other cancers.

Each committee is required to:

- Set targeted annual accrual expectations for each new clinical protocol prior to PRC submission.
- Evaluate accrual for all open studies, both clinical and non-therapeutic disease- or committee-specific.
- Close trials with poor accrual to ensure appropriate utilization of resources.
- Maintain two priority lists: 1) an ongoing priority list of all protocols under development and 2) of all protocols open or planned for each patient population.
- Review and prioritize all protocols before they are submitted to the PRC.
- Ensure that protocols UCSF develops use the same HDFCCC treatment and behavioral protocol templates to ensure the minimum set of guidelines and standards are met.
- Ensure that all review concerns are adequately addressed and the protocol is appropriately revised prior to issuing Approval.
- Review all protocol amendments before they are submitted to the PRC (amended protocols will all be required to have a summary of changes per HDFCCC standards).
- Discuss all safety issues including review of current and prior SAEs and AEs (at least weekly for Phase I or otherwise high-risk/early phase clinical trials; at least monthly for all others).
- Maintain written records of all meetings using standardized forms, including attendance and decisions concerning accrual/priorities/new concepts/protocol review.
- Prepare quarterly reports tracking the cumulative number of concepts and protocols reviewed, rejected, and accepted by the committee.
- Evaluate all new concepts. Committees must score and prioritize concepts of investigator initiated studies, and document approval status. Approved concepts will be developed into protocol format using standardized HDFCCC treatment and behavioral protocol templates to ensure the minimum set of guidelines and standards are met.

Optional oversight:

- Evaluate and monitor non-therapeutic trials.

New Protocol Review Types

Studies exempt from PRC review (see PRMS Protocol Review Committee Review Policy) can also be exempt from Program Site Committee review, although individual site committees may choose to review such studies. There is no expedited (i.e., Chair only) review format for new protocols; all must undergo full committee review. Trials that have been activated by an NCI cooperative group or the CTSU do not require review by a primary, secondary and statistical reviewer; however, these protocols must still be approved and prioritized by the full site committee. A single reviewer is assigned by the committee Chair or designee to present such trials to the committee (a cooperative

group review form is available for this purpose -- see <http://cancer.ucsf.edu/itr/itr-forms>).

New Protocol Review

A quorum is required for the conduct of every Program Site Committee meeting. Quorum is defined as 50% of the committee membership roster. Each protocol has a primary reviewer, secondary reviewer, and statistical reviewer assigned. Assignment is made by the committee Chair (or designee). Primary reviewers are required to present the protocol, and cannot be the Principal Investigator (PI). The Principal Investigator or designee is required to attend committee discussions and to answer questions, but does not present the study to the committee.

All committees will use standardized forms approved by the Director of the ITR to ensure that all required concerns are discussed consistently across all programs and disease sites. There are separate forms for primary reviews, secondary reviews, statistical reviews, cooperative group trial reviews, and the Chair or Co-Chair summary of review (see <http://cancer.ucsf.edu/itr/itr-forms>).

Primary and Secondary reviewers will provide individual scores for clinical importance, trial design, innovation/science, UCSF involvement in development, potential for UCSF publication, and accrual/feasibility. An overall score is also assigned, which takes the preceding scores into account but does not average them. The NIH scoring system will be used. After presentation by reviewers all voting members will individually score the protocol and their scores will be averaged to determine the final overall score. It is recommended that priority be given first to institutional (investigator-initiated) protocols, followed by cooperative group clinical trials and lastly to industry/pharmaceutical-sponsored clinical trials.

In addition to completing the standardized review forms, it is each committee's responsibility to provide specific information for each study. The committee will identify the following information required for PRC submissions:

- Phase of study
- UCSF involvement
- UCSF total target accrual
- UCSF target accrual per year
- Total target accrual goal if UCSF is coordinating center for multicenter trial
- Target accrual goal justification or prior accrual for similar population
- Final overall score
- All competing trials (must describe how directly competing trials will be prioritized against the trial under review; see Prioritization).
- Confirmation of submittal of all review forms, summary of review form, and numerical ranking list of all trials (see Prioritization).

In completing the above information, the Program Site Committee should be mindful that the PRC will not approve any new applications upon initial review if the projected accrual does not meet 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 by the Program Site Committee in an email to the PRC Administrator 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 Site Committee will vote on overall approval status:

1. Approval: Requires a majority vote and a final overall score of 3 or less. If the protocol is approved, the site committee can forward to the PRC for review, with all requisite information.
2. Contingent Approval: Requires a final overall score of 3 or less and will include 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.

Responses to Contingent Approval go back to the original reviewers. Each original reviewer is responsible for ensuring that all concerns are adequately responded to, ensuring that the protocol is modified appropriately, and communicating their findings to the committee Chair or designee. Once all reviews are completed, the committee Chair or designee documents the review outcome using a Contingent Response Review form (see <http://cancer.ucsf.edu/itr/itr-forms>). If there is conflict the Chair or Co-Chair should adjudicate. If the protocol gets Contingent Approval a second time, then the PI's second response goes directly to the Chair or Co-Chair for adjudication instead of going back to the original reviewers.

3. Disapproved: Includes 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. If resubmitted, these protocols are reviewed by the entire site committee.

Responses to Disapproved get placed on the next full committee agenda and are reviewed as in New Protocol Review above, the only difference being that reviews are assigned to original reviewers if they are available. If original reviewers are not available the resubmission is assigned to replacement reviewers.

Committee review outcomes will be issued by the committee Chair or Co-Chair using a standardized Summary of Review form. The Summary of Review form contains an indication of the committee's final overall score. For approved protocols, all committee review forms and the Summary of Review form with final overall score will be submitted to the PRC as part of the application. The Summary of Review form signed by the Chair or Co-Chair serves as proof of Program Site Committee approval.

New Concept Review

Site committees are required to review and discuss new institutional (investigator-initiated) concept sheets as they are developed. Concepts need to be scored and prioritized, and approval status must be documented. If approved, the committee will request that the concept be written up as a formal protocol document and will provide standardized HDFCCC protocol templates for that purpose. Once in protocol format, the study goes back to the committee for formal review as in New Protocol Review above. For those programs supported by the Investigational Trials Resource (ITR), concepts must be approved and prioritized by the site committee prior to their review by the ITR Clinical Trials Budgets Office.

Protocol Amendment Review

The review of all protocol amendments is required. Review procedures will be in line with PRC's procedures (see PRMS Amendment Submission Policy and PRMS Amendment Review Policy). Amendments are any changes made to the protocol version which was originally approved by the Program Site Committee, over the life of the clinical trial, regardless of the nature of the change (e.g., editorial, administrative, scientific, etc.). At minimum amendments should be approved by the Chair, or

designee; discussion by the entire committee or specific reviewers is at the Chair's discretion. Chair signature is required on the PRC Amendment Submission Application Form. If the Chair is the PI then the Co-Chair should sign the PRC Amendment Submission Application Form. All protocol amendments must subsequently be approved by the PRC and the institutional IRB (the Committee on Human Research, or CHR) prior to implementation. Protocols exempt from initial Program Site Committee review do not require amendment review by the Program Site Committee.

All protocol amendment applications will need to follow the PRC submission requirements. See the PRMS Amendment Submission Policy for full details.

At the Chair's discretion, approvals may be documented via summary of review forms as in New Protocol Review above. Once approved by the Program Site Committee, the amended protocol needs to be submitted to the PRC.

Safety Issues

Safety issues will be reviewed at least weekly for Phase I or otherwise high-risk or early phase clinical trials. All other trials will have safety issues reviewed at least monthly.

For investigator-initiated studies, the Principal Investigator (PI) or designee will review all applicable grades of adverse events (AEs) and serious adverse events (SAEs) prior to the meeting. This list of all AEs/SAEs along with patient status and cohort accrual (if applicable) will be presented at the meeting and the minutes will reflect the committee review. For cooperative group studies, only ADEERS reports and patient status log will be prepared. For all non-cooperative group Phase I studies, Grades 1-5 AEs and patient status log will be prepared. For all other studies, only Grades 3-5 AEs and patient status log will be prepared. The summary of AEs for all trials will be signed by the committee Chair or designee and incorporated into the minutes.

For studies initially reviewed by the Other Cancer, Early Phase Clinical Trials Unit and the Symptom Management/Palliative Care/Survivorship site committees, AE review will be conducted by the originating program, not the Program Site Committee which conducted the initial review.

Accrual Criteria

The Program Site Committees are charged with the responsibility of ensuring adequate accrual to clinical trials and for closing trials with poor accrual to ensure appropriate utilization of resources. All committees will review all enrolling studies (both clinical and non-therapeutic disease- or committee-specific) for accrual progress at least annually.

The committee is required to determine if the study should stay open. If accrual is less than projected, the committee is charged with evaluating the potential reasons for the problems and with formulating a corrective action plan which is documented in the meeting minutes. In particular, if after one year of enrollment a clinical trial has accrued less than 50% of the annual projected accrual or less than 5 patients (unless an exception has been granted), the committee will decide to either close the study or keep it open. If the intent is to keep the study open, the site committee must record a corrective action plan to indicate how it plans to improve accrual. Corrective action

plans can be submitted to the PRC in response to PRC queries. If the corrective action plan fails to increase accrual to at least 50% of the annual projected rate within six months of implementation, the committee is expected to close the study to further accrual (or terminate the study if possible). Trials accruing 50% or more of the projected annual accrual goal are re-reviewed annually until closed to enrollment.

While the Program Site Committees are charged with assessing all active protocols to ensure adequate resource usage and enrollment, and to close those not enrolling sufficiently, these committees cannot override the decision of the PRC. The ultimate recommendation for protocol closure falls under the purview of the Protocol Review Committee (see PRMS Closure Policy). Protocols allowed to continue enrollment by the relevant Program Site Committee are not exempt from annual progress and performance monitoring by the PRC (see PRMS Closure Policy).

Adjudication of Disputes

Disputes between the committee and a PI go back to the committee for review. If agreement cannot be reached there, then the dispute is referred to the Director of the Investigational Trials Resource, who will convene an ad hoc committee to carry out an appeals process. Disputes will be reviewed by the ad hoc committee within four weeks of submission.

Prioritization

Two Prioritization Lists are maintained by each site committee:

1. Overall Prioritization. To ensure adequate ongoing review of progress and performance, all new protocols, concept sheets/letters of intent, and all protocol amendments which impact the budget or accrual or are otherwise urgent will be tracked on a single list in order of priority. Each committee will numerically rank (whole numbers, please) the priority of each item relative to all other items on the list. This prioritization of all protocols and concepts within a program or committee will be re-evaluated at each site committee meeting. The protocol to undergo review by PRC should be highlighted on this list upon submission to PRC. This list will be submitted to PRC with every new protocol application, and will be used by the program or committee to determine in what order trials get attention over others. This list will also be used by the ITR to prioritize the workload for the Clinical Trials Budgets Office, Protocol Development Office, and the Regulatory Affairs Office in the ITR.
2. Prioritization of competing open and proposed protocols for each specific patient population. In addition to identifying all competing protocols for a patient population, a description of how competing trials will be prioritized is required.

Quarterly Reports

Each committee is required to submit quarterly reports to the PRC to document the cumulative number of concepts and protocols reviewed, rejected, and accepted by the committee per calendar year. A template is provided at <http://cancer.ucsf.edu/itr/itr-forms>.

Minutes

Each committee is required to maintain written minutes of all meetings, including attendance and decisions concerning accrual, priorities, new concepts, and protocol review. I.e., all reviews using standardized forms, all summary of review forms, and attendance records for each meeting will be maintained in a centralized place, and available for review.

Auditing

All Program Site Committees are subject to audit by the ITR Steering Committee to ensure compliance with Program Site Committee policies. The ITR Steering Committee will have the authority to withdraw Program Site Committee status if a committee does not satisfactorily carry out its responsibilities.

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

5/31/11

Date