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 Cancer Center Support Grant (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 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, Site Committee reviewer and review outcome forms, pertinent PRC application 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 templates; see (http://cancer.ucsf.edu/research/cores/crso#inst-trials)

- Assess general feasibility, 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 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, and assign risk level for all UCSF-initiated institutional protocols according to the HDFCCC Data Safety Monitoring Plan (DSMP), and inform the DSMC

- Provide centralized prioritization across the entire HDFCCC

- Ensure that all review concerns are adequately addressed and the protocol is appropriately revised prior to issuing initial 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 conducted at the HDFCCC and its affiliates studying patients with cancer, patients at risk for cancer, or providers of care to cancer patients require PRC review and approval prior to IRB approval. Review is either by the full committee or by the Chair or Vice Chair (expedited). The only exceptions to this requirement for PRC review are:

1) Single-patient and multi-patient expanded access protocols, as defined by the **Policy for Single and Multi-Patient Expanded Access Treatment**. In the event that the Chief Scientific Officer and the CRSO (Clinical Research Support

Office) Medical Director require a multi-patient expanded access protocol to be developed into a proper investigator initiated trial (IIT), such a protocol would require PRC review. See the **Policy for Single and Multi-Patient Expanded Access Treatment** for details. Expanded access protocols that do not meet all the criteria in 3) a-e below will still be subject to Site Committee review as per the **Policy for Single and Multi-Patient Expanded Access Treatment**.

OR

2) Studies where UCSF or its affiliates are not open to enrollment and there is no direct subject contact at UCSF or any affiliates. Examples are performing analysis on samples collected outside of UCSF or any affiliates, or performing pathology review or radiological readings for slides or images collected outside of UCSF or any affiliates.

OR

3) Those studies meeting *all* of the following criteria:

   a) the study is not funded by the NCI, does not use the NCI CIRB, and was not issued by NCTN or any other oncology cooperative group
   b) the intervention is tested on a mixture of subjects, only some but not all of whom have a cancer diagnosis
   c) none of the endpoint(s) are oncologic
   d) the subjects with a cancer diagnosis are not being treated differently than other study subjects, ***AND***
   e) the subjects with cancer will not be analyzed or reported on as a unique subset.

The same protocol cannot be submitted to PRC by separate Principal Investigators. PRC will reject any duplicate protocol submissions once identified.

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. Where there is a question on review parameters, the PRC Chair or Vice Chair adjudicates.

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. All multi-center investigator-initiated research involving treatment interventions, regardless of whether UCSF is the core or originating institution (coordinating center), are required to receive full committee review (unless they originate from another NCI-designated Cancer Center). If the grant that funds an investigator-initiated trial was peer-reviewed at the national level, HDFCCC PRC review of the trial may not be 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. If the grant that funds an investigator-initiated trial was peer-reviewed at the national level, HDFCCC PRC review of the trial may not be required.

- Prospective *Institutional* molecular or imaging diagnostic clinical trials meeting *all* of the following criteria*****:

    - contain a clearly defined hypothesis with pre-specified sample size and statistical analysis plan
    - *may* impose some risk
    - 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. With prior approval from the applicable Site Committee, and PRC and the UCSF IRB, Phase III trials that meet accrual goals may be converted to standard of care trials.

* Exceptions include testing non-cancer-specific diagnostic or therapeutic interventions within a cancer patient population, which may require only Expedited review – e.g., a flu vaccine in BMT patients.

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.

- European Organisation for Research and Treatment of Cancer (EORTC) trials.

- All multi-center investigator-initiated research originating from another NCI-designated Cancer Center (Lead Site) may receive expedited review provided the following criteria are met:

    - The Lead Site 1) has a fully approved PRMS, 2) has conducted full committee review for scientific merit, prioritization and feasibility, and 3) has issued full approval of the current protocol document
    - The Lead Site agrees to provide to the PRMS Manager with its CCSG renewal date and an assertion that its PRMS is fully approved
    - The Lead Site can provide proof of full PRMS approval to the PRMS Manager, to include documentation of the approved protocol version.

- Prospective *Institutional or Industry* molecular, genetic epidemiology, imaging diagnostic, and other research studies may undergo expedited, rather than full, committee review (even if they may impose some risk on study subjects) if they meet one of the following criteria:

    - the study does not answer specific questions about the effects or impact of particular biomedical interventions, or use the information from the diagnostic test in a manner that affects medical decision-making for the study subject
    - there is no specific hypothesis being tested, with no pre-specified sample size or statistical analysis plan (i.e., even if the information could potentially be used in medical decision-making for the study subject, but is not hypothesis-driven)
        - *Example*: broad molecular profiling efforts for which results may be shared with the treating physician or patient for possible future use in decision-making.

- Other external peer review studies also qualify if they were previously peer-reviewed by the various NIH mechanisms (e.g., R0Is, U0Is, U10s, P0Is, and P50s), other approved funding agencies meeting the NIH standard (http://cancercenters.cancer.gov/documents/NCIApprovedFundingOrganizations508C.pdf), 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. Data from multiple institutions may be pooled within the limitations of the regulations governing risk management within each institution.

- *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.

- *Industry* registry studies.

- Research studies (molecular, genetic epidemiology, imaging, diagnostic, or other) that meet all of the following criteria:

    - impose minimal risk on subjects (as per the UCSF IRB definitions – see Minimal Risk Tip Sheet, http://irb.ucsf.edu/levels-review)
    - *do not* answer specific questions about the effects or impact of particular biomedical interventions
    - *do not* use information from a diagnostic test, that could affect medical decision-making for the study subject.
        - *Example*: a study whose objective is only the gathering of data on the characteristics of a new diagnostic approach.

- *Institutional or Industry* 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 (and queries incomplete submissions), assigns all complete submissions to a statistician not involved in the study development and design of the protocol, 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, Site Committee reviewer and review outcome forms, pertinent PRC application information, and, as applicable, investigator's brochure[s], surveys, quality of life questionnaires, other tools, and letters of support). Required Site Committee reviewer forms differ by protocol type, and are outlined in the **PRMS Site Committee Review Policy**.

The PRC full committee review forms consist of a combination of check-boxes, tables 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*, is feasibility appropriately addressed, identify potential conflicts, funding source appropriate, can the study complete in a reasonable time?
- *Protocol*: Statistical plan assessment, are objectives scientifically sound, will study design meet objectives, and does the science justify the risks?
- *Study Design*: Can the study design answer the statistical question?
- *Statistical Design*: Is the statistical design appropriate, endpoints adequate, and the sample size calculation/power sufficient?
- *Data Safety Monitoring*: Assign risk level on all UCSF-initiated institutional protocols (per the HDFCCC DSMP). Is DSMC and/or DSMP necessary and included, does protocol contain adequate monitoring and surveillance, and are safety/efficacy interim analyses and formal stopping rules necessary and included?
- *Analysis Plan*: Are planned analyses appropriate?
- *Children, Women and Minorities*: Is an inclusion plan for each group necessary and included?
- *Final Scientific Score*: Does the reviewer agree with the Site Committee score, and what is the reviewer's recommendation for a Final Scientific Score 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 Site Committee is required to numerically rank each submitted protocol in relation to all other new protocols, concept sheets/letters of intent, and all protocol amendments which impact the budget or accrual or are otherwise urgent from that 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. Site Committees are also required to always submit a list covering all patient populations applicable to that committee, to include all open or planned protocols competing for each population (even if there are no competing trials pertaining to the protocol under review). Competing trials should identify all applicable protocols impacting the disease area, not just those from within the applicable Site Committee. 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 or exceeds the accrual projection requirements in **Table 1** below:

Table 1 – Required Minimum Annual Accrual

Type of Trial	Conventional Trial	Rare Cancer Status, Molecularly Defined Subsets, Unique Correlative Science
Institutional Single Center	5	3*
Institutional Multi- Center (includes multi-center consortia led by other centers)	5	1*
Cooperative Group/ National Group	3	1*
Industry	5	1*

*Waiver requests at the time of PRC review are allowed for these studies. Requests for waivers are submitted electronically by the Site Committee in an email to the PRC Administrator and must justify why it is necessary to open such a low accruing study. (The PRC may independently determine that a waiver is warranted, either at initial review or at annual review; the PRC Administrator will automatically issue waivers for Pediatrics studies.) Waivers to these requirements can be granted on a case by case basis by the PRC, provided one of the following three criteria are met:

1. The disease being studied represents a rare cancer, consisting of a malignancy with an annual incidence in the U.S.A. of <10,000 new cases.

2. Molecularly defined subsets may be considered as rare cancers if there is a clear mechanistic rationale why the study treatment is predicated on that specific molecular characteristic.

3. Unique correlative science will be undertaken by a UCSF investigator that will be informative even with a small number of UCSF accruals.

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. If the PRC determines at annual review that a waiver is applicable, the decision does not impact review processes. The PRC Administrator checks for accrual criteria and for waiver requests, and ensures and documents PRC approval of waiver requests. Any new protocols not meeting the minimum accrual criteria in **Table 1** which do not have approved waiver requests in place will not be processed for formal PRC review.

Each reviewer considers the Site Committee reviewer and summary of review forms, and all other submitted documents including the protocol and all pertinent PRC application information. (Required Site Committee reviewer forms differ by protocol type, and are outlined in the **PRMS Site Committee Review Policy**.) Each reviewer

then completes the PRC full committee review form as above, which includes scoring using the NIH scale. Primary and Secondary reviewers score across a variety of domains (clinical importance, trial design, innovation/science, statistics, DSMP, competing trials, and accrual/feasibility) and recommend a Final Scientific Score (not an average) for each trial. The reviewing biostatistician provides an overall score as well. Non-reviewing members do not score.

A quorum is required for the conduct of every PRC meeting. Quorum is defined as a minimum of 8 reviewers to start the meeting. 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 Overall Scientific Score for each trial is determined by averaging the scores from all assigned reviewers. 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)

The primary reviewer identifies the level of risk for all UCSF-initiated institutional protocols according to the table in the HDFCCC DSMP, and the PRC Administrator notifies the DSMC Manager of the determined risk level; the DSMC Manager assigns rigorous monitoring to all trials identified as high risk, as per the HDFCCC DSMP.

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, regardless of the type of protocol disposition (see below). Approval notifications and review outcome memos will include the committee's Overall Scientific Score.

Exceptions: Phase 3 Industry 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 may qualify for an accelerated full committee review, called Ad Hoc Full. The PRC Chair or Vice Chair will make the determination on a case-by-case basis; if allowed an Ad Hoc Full review, the review will take place outside of the formal full committee meeting. Once a qualifying protocol is ready for review (all queries addressed), the PRC Chair or Vice Chair will assign one Primary reviewer and the Biostatistical Core Director or PRC Administrator will assign one biostatistician to review the protocol; assignments will attempt to even out the workload among members by either assigning to those who cannot attend the meeting, or assigning to those members who have reviewed the least number of protocols throughout the year. All review processes as outlined above for full committee review also apply to these Ad Hoc Full reviews. The PRC Administrator will create and disseminate the standard review documents to the assigned reviewers in real time; the

reviewers will have up to two weeks to review and submit their findings. Findings will be discussed via email between the assigned reviewers, PRC Chair and Vice Chair, PRMS Manager and PRC Administrator, and reviewers will finalize their full committee review forms in the secure electronic web-based database. If any reviewer has significant concerns, the protocol will be placed on the next full committee meeting agenda for full discussion. Once all reviews are complete, the PRC Administrator will draft the minutes, the PRC Chair or Vice Chair will approve, and the PRC Administrator will issue the approval notification and review outcome memo with final score.

Protocol Disposition Based on Review Outcome

1. *Approved*

If the protocol is approved, no further action is necessary until the protocol is amended. A review outcome memo indicating approval is created and sent to the study PI.

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. 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 and that the protocol is revised appropriately.

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 final adjudication instead of going back to the original reviewers.

Once the protocol is approved, a review outcome memo indicating approval is created and sent to the study PI.

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. 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.

Once the protocol is approved, a review outcome memo indicating approval is created and sent to the study PI.

Replacement of Assigned Reviewers

If an assigned full committee reviewer declines attendance far enough in advance of the meeting, the Chair or Vice Chair will reassign the protocol to another reviewer. If an assigned reviewer is expected to attend but does not show up for the meeting and fails to complete a review, then the absentee reviewer is replaced with the Chair or Vice Chair, depending on who is officiating at the meeting. In such cases, the Chair or Vice Chair completes a review using the role of the missing reviewer (either primary, secondary, or statistician).

If an original reviewer is unavailable for assignment to a Contingent Response review or Disapproved re-review, a replacement reviewer with the same review role is assigned by the Chair or Vice Chair.

If following assignment to a Contingent Response review, an assigned reviewer is delinquent or absentee for any reason (examples include leaving the institution, extended absence due to travel or medical leave, or failure to respond in a reasonable time period) so that the review outcome cannot be established, that reviewer will be replaced with the Chair or Vice Chair. This will be at the discretion of the Chair, Vice Chair, PRMS Manager or PRC Administrator. The Chair or Vice Chair will complete a review using the role of the missing reviewer (either primary, secondary, or statistician).

New Protocols -- Expedited Review

Expedited studies are submitted and reviewed for completeness by the PRC Administrator. Submissions should include all applicable 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 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 **Table 1** 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. If concerns are not met appropriately, the Chair or Vice Chair sends it to full committee, where it will be reviewed as in New Protocols -- Full Committee Review above.

Centralized Prioritization

Effective 2014, the PRC is responsible for prioritizing all full committee and expedited new protocol reviews across the entire HDFCCC. Exempt trials are not prioritized. All applicable trials reviewed before January 2014 (and not yet Open to Accrual) were placed on the list in chronological order (using PRC submission date), and split into tertiles, the oldest tertile being prioritized as First Tertile, the middle tertile as Second Tertile, and the youngest tertile as Third Tertile.

Currently, all applicable new studies on each meeting's agenda are prioritized as:

- First Septile (generally Pre-Clinical Discovery ISTs)
- Second Septile (generally Peer-Review Funded ISTs)
- Third Septile (generally all other ISTs)
- Fourth Septile (generally Cooperative/National Group *with* Leadership Role)
- Fifth Septile (generally Cooperative/National Group *without* Leadership Role)
- Sixth Septile (generally Industry *with* Leadership Role)
- Seventh Septile (generally Industry *without* Leadership Role).

New studies are added to the bottom of whichever septile is applicable (or, if the committee feels strongly about a particular trial, they may indicate precisely where a new trial should be placed within a particular septile). Where there is more than one trial to insert into a sepile, the PRC submission date is used to determine the order in which they are placed within the septile. If there is more than one trial with the same prioritization and the same PRC submission date, then the committee is asked to determine which gets listed above the other. Full committee trials reviewed at the meeting are prioritized by the committee; expedited trials reviewed since the prior meeting (going back to the day after the prior meeting) are prioritized by the Chair or Vice Chair. In general, Institutional and National Group trials will take precedence over Industry, but the quality of the science and impact of the trial, as well as UCSF's role in the trial, will be taken into account; having a small number of slots for which to enroll will not necessarily place a study in the First Septile. Members take into account the Site Committee prioritization list, the Site Committee Final Overall Score, the PRC Overall Scientific Score, and protocol type (Institutional, Industry, National Group, External Peer Reviewed), as well as any other extenuating factors deemed applicable.

The list is reassessed at each meeting. Once protocols are Open to Accrual (or Abandoned) they are removed from the list. The list is shared with the HDFCCC Deputy Director, HDFCCC Director of Finance and Operations, and HDFCCC Director of Scientific Programs Administration.

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

New submissions, whether queried before or following formal PRC review, are given three months in which to respond to the query. Response can consist of an answer to a query issued prior to assignment for review, or answering a Contingent Response or Disapproved query requesting response to formal PRC findings. New unapproved protocols without a response three months from the time of original query 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 file a response to the review outcome query by indicating their wish to withdraw the submission and supplying the reason for withdrawal.

Progress and Performance Monitoring

All enrolling studies are monitored at least annually for scientific progress and accrual objectives, both by the Site Committees and the PRC. 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. Site Committees are required to either close poorly accruing studies or develop corrective action plans. Site Committee procedures are described under the **PRMS 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 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 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.

PRMS Reliance

As per NOT-CA-16-038, https://grants.nih.gov/grants/guide/notice-files/NOT-CA-16-038.html), and on a case-by-case basis, the HDFCCC may choose to rely on the Lead Site's full committee PRMS review for multi-center investigator-initiated research protocols originating from other NCI-designated Cancer Centers. In all such cases, the core or originating institution (coordinating center, or Lead Site) must meet the following criteria:

- The Lead Site 1) has a fully approved PRMS, 2) has conducted a full committee review for scientific merit, prioritization and feasibility, and 3) has issued their full approval of the protocol document

- The Lead Site agrees to provide to the PRMS Manager with its CCSG renewal date and an assertion that its PRMS is fully approved
- The Lead Site can provide proof of full PRMS approval to the PRMS Manager, to include documentation of the approved protocol version.

When all the above criteria are met, the HDFCCC PRC may perform an expedited review. Where the Lead Site's PRMS does not have full approval, the HDFCCC PRC must conduct full committee review. The HDFCCC PRC may still choose to conduct a full committee review regardless of whether all the above criteria have been met.

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 Chair will review the reports, and may forward to full committee for discussion.

Review Conflicts

PRC members cannot be assigned to review protocols for which they act as PI or have had any study design input.

On all studies where the PI is also the committee Chair, it is considered a conflict and the Chair is prohibited from performing related committee business. In all such cases the Chair should defer to the Vice Chair to conduct all related committee business, and the Vice Chair is expected to complete and sign all applicable review forms. This applies to new protocol reviews, protocol amendment reviews, and assignment of reviewers. Likewise, if the Chair is unavailable and the Vice Chair is the PI, review must be delayed until the Chair becomes available; the Vice Chair should not conduct committee business pertaining to a study for which the Vice Chair is PI.

On all expedited studies where the committee Chair is also the PI, or has performed a review at Site Committee, it is considered a conflict and the Chair is prohibited from performing related committee business. In all such cases the Chair should defer to the Vice Chair to conduct the expedited review. Likewise, if the Chair is unavailable and the Vice Chair is the PI, or has performed a review at Site Committee, review must be delayed until the Chair becomes available; the Vice Chair should not conduct the expedited review.

Response Evaluation

The PRC Chair periodically spot-checks PRC reviewer assessments of Contingent Approval responses to ensure that all concerns requiring a response were addressed adequately and that all necessary protocol modifications were evaluated and accounted for before initial approval was granted. The PRC Chair is assigned to review a Contingent Approval response, and completes a review assessment checklist to document any concerns that should have been more completely addressed, or any protocol modifications that should have been made but were not. Results from these assessments are saved to the server and used to work with deficient reviewers on strengthening their reviews.

Alternate Procedure

None.

Policy Approval

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

Eric Small, MD
Deputy Director,
Helen Diller Family Comprehensive Cancer Center

5.3.19
Date

Jennifer Clarke, MD
Chair, Protocol Review Committee

5/3/19
Date

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

Policy Revision Summary of Changes

Policy Title:	**PRMS Protocol Review Committee (PRC) Review Policy**
Version Date:	May 2, 2019
Version Number:	Revision 12

Notes: Page number corresponds to page number in updated version (Revision 12). New text in modified paragraphs is shown as ***bold italics*** and deleted text is shown as ~~strikethrough~~.

Page No.: All pages	**Section**: Footer
Original Text	Revision 11 12/04/2018
New Text	Revision 1~~1~~***2*** ~~12~~***05***/04***2***/201~~8~~***9***
Reason for Change	To reflect updated version number and date.

Page No.: 2	**Section**: Procedures New Protocol Review Types
Original Text	All clinical trials conducted at the HDFCCC and its affiliates studying patients with cancer, patients at risk for cancer, or providers of care to cancer patients require PRC review and approval prior to IRB approval. Review is either by the full committee or by the Chair or Vice Chair (expedited). The only exceptions to this requirement for PRC review are those studies meeting *all* of the following criteria: a) the intervention is tested on a mixture of subjects, only some but not all of whom have a cancer diagnosis b) none of the endpoint(s) are oncologic c) the subjects with a cancer diagnosis are not being treated differently than other study subjects, ***AND*** d) the subjects with cancer will not be analyzed or reported on as a unique.

New Text	All clinical trials conducted at the HDFCCC and its affiliates studying patients with cancer, patients at risk for cancer, or providers of care to cancer patients require PRC review and approval prior to IRB approval. Review is either by the full committee or by the Chair or Vice Chair (expedited). The only exceptions to this requirement for PRC review are***:*** ***1) Single-patient and multi-patient expanded access protocols, as defined by the Policy for Single and Multi-Patient Expanded Access Treatment. In the event that the Chief Scientific Officer and the CRSO (Clinical Research Support Office) Medical Director require a multi-patient expanded access protocol to be developed into a proper investigator initiated trial (IIT), such a protocol would require PRC review. See the Policy for Single and Multi-Patient Expanded Access Treatment for details. Expanded access protocols that do not meet all the criteria in 3) a-e below will still be subject to Site Committee review as per the Policy for Single and Multi-Patient Expanded Access Treatment.*** ***OR*** ***2) Studies where UCSF or its affiliates are not open to enrollment and there is no direct subject contact at UCSF or any affiliates. Examples are performing analysis on samples collected outside of UCSF or any affiliates, or performing pathology review or radiological readings for slides or images collected outside of UCSF or any affiliates.*** ***OR*** 3) ***T***~~t~~hose studies meeting *all* of the following criteria: a) ***the study is not funded by the NCI, does not use the NCI CIRB, and was not issued by NCTN or any other oncology cooperative group*** ***b)*** the intervention is tested on a mixture of subjects, only some but not all of whom have a cancer diagnosis ***c***~~b~~) none of the endpoint(s) are oncologic ***d***~~c~~) the subjects with a cancer diagnosis are not being treated differently than other study subjects, ***AND*** ***e***~~d~~) the subjects with cancer will not be analyzed or reported on as a unique.
Reason for Change	Addition of two new categories of non-oncologic trials; clarification added on the previously existing (now third) category of non-oncologic trials.

Page No.: 5	**Section**: Procedures New Protocol Review Types
Original Text	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.
New Text	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. • ***European Organisation for Research and Treatment of Cancer (EORTC) trials.***
Reason for Change	Added new expedited review category for EORTC trials, which are classified as Institutional but treated as cooperative group trials due to extensive peer review.

Page No.: 5	**Section**: Procedures New Protocol Review Types
Original Text	• Single-subject compassionate use or emergency use protocols: expedited review is required at PRC; however, Site Committees are exempted from performing formal expedited review and can follow the alternate review process outlined in Alternate Procedure below. • *Institutional or Industry* expanded access or compassionate use protocols designed to enroll multiple subjects: these protocols *must* receive expedited review at both Site Committee and PRC; the Alternate Procedure noted below *does not apply*.
New Text	• ~~Single-subject compassionate use or emergency use protocols: expedited review is required at PRC; however, Site Committees are exempted from performing formal expedited review and can follow the alternate review process outlined in Alternate Procedure below.~~ • ~~*Institutional or Industry* expanded access or compassionate use protocols designed to enroll multiple subjects: these protocols *must* receive expedited review at both Site Committee and PRC; the Alternate Procedure noted below *does not apply*.~~
Reason for Change	Deleted single-subject and multi-subject compassionate use/emergency use protocols from the studies requiring expedited review section, as both are now considered non-oncologic and do not undergo PRC review.

Page No.: 6-7	**Section**: Procedures New Protocols – Full Committee Review
Original Text	• General and Feasibility Review: Are the investigators appropriate, are competing protocols prioritized*, is feasibility appropriately addressed, identify potential conflicts, funding source appropriate, can the study complete in a reasonable time? • Protocol: Statistical plan assessment, are objectives scientifically sound, will study design meet objectives, and does the science justify the risks? • Study Design: Can the study design answer the statistical question? • Statistical Design: Is the statistical design appropriate, endpoints adequate, and the sample size calculation/power sufficient? • Data Safety Monitoring: Assign risk level on all UCSF-initiated institutional protocols (per the HDFCCC DSMP). Is DSMC and/or DSMP necessary and included, does protocol contain adequate monitoring and surveillance, and are safety/efficacy interim analyses and formal stopping rules necessary and included? • Analysis Plan: Are planned analyses appropriate? • Children, Women and Minorities: Is an inclusion plan for each group necessary and included? • Final Scientific Score: Does the reviewer agree with the Site Committee score, and what is the reviewer's recommendation for a Final Scientific Score for the protocol? • Review Outcome: List concerns requiring response and review outcome recommendation (Approved, Contingent Approval, or Disapproved).

New Text	• ***General and Feasibility Review***: Are the investigators appropriate, are competing protocols prioritized*, is feasibility appropriately addressed, identify potential conflicts, funding source appropriate, can the study complete in a reasonable time? • ***Protocol***: Statistical plan assessment, are objectives scientifically sound, will study design meet objectives, and does the science justify the risks? • ***Study Design***: Can the study design answer the statistical question? • ***Statistical Design***: Is the statistical design appropriate, endpoints adequate, and the sample size calculation/power sufficient? • ***Data Safety Monitoring***: Assign risk level on all UCSF-initiated institutional protocols (per the HDFCCC DSMP). Is DSMC and/or DSMP necessary and included, does protocol contain adequate monitoring and surveillance, and are safety/efficacy interim analyses and formal stopping rules necessary and included? • ***Analysis Plan***: Are planned analyses appropriate? • ***Children, Women and Minorities***: Is an inclusion plan for each group necessary and included? • ***Final Scientific Score***: Does the reviewer agree with the Site Committee score, and what is the reviewer's recommendation for a Final Scientific Score for the protocol? • ***Review Outcome***: List concerns requiring response and review outcome recommendation (Approved, Contingent Approval, or Disapproved).
Reason for Change	Italicized existing underlined text to avoid confusion with other underlined section headers.

Page No.: 7	**Section**: Procedures New Protocols – Full Committee Review
Original Text	* 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 Site Committee is required to numerically rank each submitted protocol in relation to all other new protocols, concept sheets/letters of intent, and all protocol amendments which impact the budget or accrual or are otherwise urgent from that 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. Site Committees are also required to always submit a list covering all patient populations applicable to that committee, to include all open or planned protocols competing for each population (even if there are no competing trials pertaining to the protocol under review). Competing trials should identify all applicable protocols impacting the disease area, not just those from within the applicable Site Committee. 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 or exceeds the accrual projection requirements in **Table 1** below:
New Text	* ***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 Site Committee is required to numerically rank each submitted protocol in relation to all other new protocols, concept sheets/letters of intent, and all protocol amendments which impact the budget or accrual or are otherwise urgent from that 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. Site Committees are also required to always submit a list covering all patient populations applicable to that committee, to include all open or planned protocols competing for each population (even if there are no competing trials pertaining to the protocol under review). Competing trials should identify all applicable protocols impacting the disease area, not just those from within the applicable Site Committee. 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 or exceeds the accrual projection requirements in **Table 1** below:
Reason for Change	Italicized existing underlined text to avoid confusion with other underlined section headers.

Page No.: 9	**Section**: Procedures New Protocols – Full Committee Review
Original Text	In addition to the above, the PRC Chair or Vice Chair assesses all full committee reviews for eligibility for Early Phase Clinical Research Support (EPCRS) funding, by identifying those protocols which are institutional, interventional, Phase I and will complete within 1-2 years. The PRC Administrator notifies the Scientific Programs Administration Office of any study meeting all four criteria; it is the responsibility of the Scientific Programs Administration Office to elicit a formal EPCRS funding application from the PI of the protocol.
New Text	~~In addition to the above, the PRC Chair or Vice Chair assesses all full committee reviews for eligibility for Early Phase Clinical Research Support (EPCRS) funding, by identifying those protocols which are institutional, interventional, Phase I and will complete within 1-2 years. The PRC Administrator notifies the Scientific Programs Administration Office of any study meeting all four criteria; it is the responsibility of the Scientific Programs Administration Office to elicit a formal EPCRS funding application from the PI of the protocol.~~
Reason for Change	Deleted paragraph to match current practice. EPCRS is no longer a CCSG funding mechanism, so PRC no longer makes this assessment.

Page No.: 9	**Section**: Procedures New Protocols – Full Committee Review
Original Text	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, regardless of the type of protocol disposition (see below). Approval notifications and review outcome memos will include the committee's Overall Scientific Score.

New Text	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, regardless of the type of protocol disposition (see below). Approval notifications and review outcome memos will include the committee's Overall Scientific Score. **<u>Exceptions</u>: Phase 3 Industry 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 may qualify for an accelerated full committee review, called Ad Hoc Full. The PRC Chair or Vice Chair will make the determination on a case-by-case basis; if allowed an Ad Hoc Full review, the review will take place outside of the formal full committee meeting. Once a qualifying protocol is ready for review (all queries addressed), the PRC Chair or Vice Chair will assign one Primary reviewer and the Biostatistical Core Director or PRC Administrator will assign one biostatistician to review the protocol; assignments will attempt to even out the workload among members by either assigning to those who cannot attend the meeting, or assigning to those members who have reviewed the least number of protocols throughout the year. All review processes as outlined above for full committee review also apply to these an Ad Hoc Full reviews. The PRC Administrator will create and disseminate the standard review documents to the assigned reviewers in real time; the reviewers will have up to two weeks to review and submit their findings. Findings will be discussed via email between the assigned reviewers, PRC Chair and Vice Chair, PRMS Manager and PRC Administrator, and reviewers will finalize their full committee review forms in the secure electronic web-based database. If any reviewer has significant concerns, the protocol will be placed on the next full committee meeting agenda for full discussion. Once all reviews are complete, the PRC Administrator will draft the minutes, the PRC Chair or Vice Chair will approve, and the PRC Administrator will issue the approval notification and review outcome memo with final score.**
Reason for Change	Added new text to the full committee review process to outline new ad hoc full committee review procedure for Phase III Industry studies. Studies will not take up agenda slots, but are still considered Full Committee reviews. To be reviewed outside of PRC meetings, with just Primary and Biostatistical (and Chair/Vice Chair) review; same PRC forms will be used, and minutes will be approved in the same manner as studies reviewed in meetings. The only difference is there will be no Secondary review, and any discussion of points of concern will be conducted via email.

Page No.: 9	**Section**: Procedures New Protocols – Full Committee Review
Original Text	Protocol Disposition Based on Review Outcome 1. Approved If the protocol is approved, no further action is necessary until the protocol is amended. A review outcome memo indicating approval is created and sent to the study PI. 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. Responses are filed in the secure electronic web-based database by either the PI or designee.
New Text	***Protocol Disposition Based on Review Outcome*** 1. ***Approved*** If the protocol is approved, no further action is necessary until the protocol is amended. A review outcome memo indicating approval is created and sent to the study PI. 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. Responses are filed in the secure electronic web-based database by either the PI or designee.
Reason for Change	Italicized existing underlined text to avoid confusion with other underlined section headers.

Page No.: 10	**Section**: Procedures New Protocols – Full Committee Review
Original Text	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. Responses are filed in the secure electronic web-based database by either the PI or designee.
New Text	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. Responses are filed in the secure electronic web-based database by either the PI or designee.
Reason for Change	Italicized existing underlined text to avoid confusion with other underlined section headers.

Page No.: 14	**Section**: Procedures Alternate Procedure
Original Text	Emergency use and compassionate use protocols designed to treat only a ***single patient*** do not have to undergo formal Site Committee review. The Site Committee need only complete the following: • Chair or Co-Chair signoff on the Single-Patient Emergency/Compassionate Use Chair/Co-Chair Review form. The Site Committee does not need to prepare any Protocols in Development or Competing Trials lists. Applicants to PRC will still need to perform ePRMS OnCore entry/application as with any other protocol; PRC will accept the FDA Form 3926 in lieu of a protocol document. Once submitted to PRC, the PRC Chair will perform an expedited review. Compassionate use protocols or treatment extension protocols that may enroll multiple patients still require expedited review at both Site Committee and PRC; the Alternate Procedure noted above *does not apply* to such studies.
New Text	~~Emergency use and compassionate use protocols designed to treat only a ***single patient*** do not have to undergo formal Site Committee review. The Site Committee need only complete the following:~~ ~~• Chair or Co-Chair signoff on the Single-Patient Emergency/Compassionate Use Chair/Co-Chair Review form.~~ ~~The Site Committee does not need to prepare any Protocols in Development or Competing Trials lists. Applicants to PRC will still need to perform ePRMS OnCore entry/application as with any other protocol; PRC will accept the FDA Form 3926 in lieu of a protocol document. Once submitted to PRC, the PRC Chair will perform an expedited review.~~ ~~Compassionate use protocols or treatment extension protocols that may enroll multiple patients still require expedited review at both Site Committee and PRC; the Alternate Procedure noted above *does not apply* to such studies.~~
Reason for Change	Deleted single-subject and multi-subject compassionate use/emergency use protocols from the Alternate Procedure section, as both are now considered non-oncologic and do not undergo PRC review.