UCSF Helen Diller Family Comprehensive Cancer Center

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

PRMS Protocol Closure Policy

PRMS Procedure for Closing Studies for

Poor Accrual or Outdated Scientific Relevance

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Purpose

The purpose of this policy is to document the process by which studies are monitored by both the Site Committees and the Protocol Review and Monitoring Committee (PRMC) for possible closure for poor accrual or outdated scientific relevance.

Scope

This policy applies to all faculty and staff serving on and supporting the Protocol Review and Monitoring System (PRMS) which includes Site Committee and PRMC.

Definitions

Protocol Review and Monitoring Committee (PRMC): The centralized review committee which carries out final scientific and feasibility review, and prioritization of studies across the Helen Diller Family Comprehensive Cancer Center (HDFCCC).

Protocol Review and Monitoring Systems (PRMS): The HDFCCC organizational unit responsible for scientific and feasibility review, and prioritization of studies across the HDFCCC. PRMS activities include a two-stage review of protocols, first at the Site Committee level and second, centrally through the PRMC.

Site Committees: Disease-, discipline-, or location-specific clinical research working groups consisting of faculty members, clinical research staff and support staff (e.g., pharmacy, nursing) charged with oversight of all clinical research studies in the designated research area. Site Committees are responsible for the first stage of scientific and feasibility protocol review, and protocol conduct and monitoring. Complete PRMS responsibilities of the site committee are detailed in the PRMS Site Committee Review Policy. Site Committees also are responsible for protocol development and activation, undertaken in coordination with the Clinical Research Support Office (CRSO), and for any subsequent protocol audits and monitoring, undertaken in coordination with the Data and Safety Monitoring Committee (DSMC). Site Committees will also interface with UCSF clinical research network sites, in coordination with the Clinical Research Network Office (CRNO).

Background

Per Cancer Center Support Grant (CCSG) Guidelines, Centers involved in clinical research are required to have a mechanism for assuring adequate internal oversight of the conduct of all cancer clinical studies in the institution or institutions that formally comprise the Center. The focus of the PRMS is on *scientific merit, priorities and progress* of the clinical research in the Center. The PRMS has 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. The NCI requires that the PRMS monitor protocols for progress and performance at least annually and close those accruing poorly or with outdated scientific relevance.

PRMS responsibilities at the HDFCCC are carried out on two separate levels to ensure optimal oversight of progress and performance. Site Committees are expected to review accrual and scientific merit regularly and to close protocols that do not meet appropriate thresholds. In addition, the Protocol Review and Monitoring Committee (PRMC) independently reviews accrual and scientific merit of all open protocols at least annually.

Procedures

1.0 Site Committee Initiated Review

As specified in the PRMS Site Committee Review Policy, Site Committees are expected to review accrual to ensure that studies are on target to complete in a reasonable timeframe and that underrepresented populations are included. Protocols which the Site Committee decides to close are recorded in the Cancer Center's electronic database (hereafter referred to as the CTMS, or Clinical Trials Management System) but do not undergo review by the PRMC once they are closed.

If the Site Committee wants a protocol to remain open to accrual, the Site Committee should formulate a corrective action plan to improve accrual. If at the next accrual review the protocol has not made progress toward the minimum accrual threshold in **Table 1**, the Site Committee is expected to close the protocol to further accrual (and terminate the study, if possible). It is not required that these corrective action plans be reported to the PRMC. However, when the PRMC conducts its independent review as described below in PRMC Initiated Review, should it request a response to its concerns (including a corrective action plan), the Site Committee can submit its existing corrective action plan (if still valid) in response to the PRMC.

2.0 PRMC Initiated Review

Studies are monitored for progress and performance via Continuation Reviews at least annually once they are Open to Accrual in the CTMS. Studies with zero accruals and no waiver granted are first monitored at six months (see Exceptions below); all others are first monitored at one year. Therefore, once a protocol is open to enrollment, it is assigned a Renewal Date of six months post Open to Enrollment date; this is the date that initially drives Continuation Reviews.

Prior to each PRMC meeting, the PRMC Administrator identifies all open protocols which are *not* PRMC Exempt and require review (termed "Continuation Review" in the CTMS). Protocols eligible for review at each meeting include:

- All protocols open for six months with zero accruals, no waiver in place, and no temporary closures greater than three months;
- All other protocols that are open to enrollment for at least one year;
- Re-reviews ordered by the Chair/Vice Chair or committee on prior annual review; or,
- Ad hoc reviews as requested by the PRMC Chair. Ad hoc reviews may be requested by the PRMC Chair if concerns have been raised about scientific validity, safety or accrual trends seen in HDFCCC or NCI reports (e.g., Data Table 4).

2.1 PRMC Review Process

Once identified and placed on the agenda, the following data is collected from the CTMS for each identified study:

- Study Number
- PI Name
- Study Title
- Primary Objective
- Study Phase

- Sponsor
- Date Opened to Accrual
- Any temporary closure and re-opened dates
- PRMC Annual Review (Continuing Review) Renewal Date
- Review Type (6-Month Zero Accrual, Initial, Annual, 6-Month Follow-Up, Ad Hoc)
- Waiver and National Chair Information
- Protocol (Total) Target Accrual Figure
- Anticipated Annual Accrual Rate
- Actual Accrual Rate for the Last Year
- Total Target Accrual Figure
- Total Accrual Figure to Date

Graphs are created by the PRMS Administrator to trend the projected accrual vs. actual accrual for the duration of the study.

Along with the above data, the minimum annual accrual requirements found in **Table 1** below are considered.

Table 1 – Required Minimum Annual Accrual

Type of Study	Conventional Study	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*

* Waivers to this requirement can be granted by the PRMC Chair at the time of PRMC initial protocol review, or by the PRMC Chair or Vice Chair during the annual review process. If the PI's response to a Continuation Review includes a waiver request, those may be granted by the PRMC Chair/Vice Chair. The PRMC Administrator ensures appropriate documentation in the CTMS for all PRMC approval of waivers; Pediatric protocol waivers for rare cancer are automatically granted by the PRMC Administrator.

Waiver definitions can be found in the **PRMS Protocol Review and Monitoring Committee (PRMC) Review Policy**.

Prior to the meeting the Chair or Vice Chair reviews accrual and scientific relevance for all protocols placed on the agenda, and makes a determination to either approve, close to further accrual, request a PI response to unacceptable findings, or forward to full committee for discussion and determination.

At the meeting, the full committee deliberates on accrual and scientific relevance for all protocols forwarded by the Chair or Vice Chair, with the same possible outcomes: approve; close to further accrual; or request a PI response to unacceptable findings.

- Approve: If the accrual and scientific relevance are found acceptable, the study is approved for six months or one year from the date of initial review of this continuation review cycle (i.e., the date of the meeting).

- Closed by PRMC: If the accrual or scientific relevance are found unacceptable, the first of two options is for the PRMC to close the study to further accrual. Correspondence detailing the PRMC's decision to close is sent to the UCSF PI and the relevant Site Committee Chair or Co-Chair. Upon release of the correspondence to the PI and relevant Site Committee Chair or Co-Chair, the PRMC changes the study status to Closed to Accrual. The PI may submit an appeal – see **Appeals to PRMC Closure** below.

- Request a PI Response: If the accrual or scientific relevance are found unacceptable, the second of two options is for the PRMC to request a response without closing to further accrual. The protocol/local site PI and the relevant Site Committee Chair or Co-Chair are notified about the issue(s) and requested to provide a response. Notification requires the following information as applicable (differs depending on whether the finding is low accrual, accrual targets not met, or poor scientific relevance):

- Whether the annual target accrual goal was met
- Whether accrual figures in the CTMS are accurate
- Whether there are participants on study treatment (and if yes, the plan for those participants)
- Whether the study is or will be closed to accrual
- Whether the study is or will be terminated at the IRB (IRB Study Closure)
- Whether there are extenuating circumstances that can be resolved with a revised recruitment action plan (which must be included with the response) and if relevant, whether the study still has scientific relevance.

The Site Committee Administrator and CRSO leadership will help in following up with the PI to ensure a response is submitted within 30 days. If no response is received within 30 days, the PRMC closes the study to further accrual.

All responses received are placed on the agenda of the next scheduled PRMC meeting, and reviewed by the Chair or Vice Chair in advance of the meeting. The Chair or Vice Chair makes a determination to either approve or close to further accrual, or forward to full committee for discussion and determination. Site Committee Chair and Co-Chair responses can be accepted

in place of a PI response. If the study will not be closed or retired by the study team, the response is assessed as follows:

- If the PRMC agrees with the response, then depending on the corrective action plan provided and at the PRMC Chair's discretion, the study is approved for six months or one year from the date of initial review of this continuation review cycle.
- If the PRMC does not agree with the response, it closes the study to further accrual. Correspondence detailing the PRMC's closure to further accrual is sent to the protocol/local site PI and the relevant Site Committee Chair or Co-Chair. The PI has the option to submit an appeal – see **Appeals to PRMC Closure** below.

Exceptions to the above process:

- All zero accrual protocols identified by the PRMC Administrator at six months with no waivers in place and no temporary closures greater than three months receive a Continuation Review with an outcome of Approved, but are sent a letter warning the PI that if there are still zero accruals at one year, the study *will* be closed.
    - Studies with waivers in place which allow a minimum of 3 accruals per year will also receive warning letters if they have zero accruals at six months.
    - At one year, if there are still zero accruals without significant temporary closures, the study is closed.
- PRMC does *not* perform reviews on PRMC Exempt protocols and Departmental Reliance protocols.

3.0 Appeals to PRMC Closure

After the PRMC issues its decision to close to further accrual, the PI or Site Committee Chair or Co-Chair has the option to appeal. If the PI or Site Committee Chair or Co-Chair appeals to the PRMC, then the protocol is referred to the PRMC Chair for adjudication. The PRMC Chair either approves the appeal, or keeps the study closed. If the appeal is approved, the PRMC Administrator changes the study status to Open to Accrual.

4.0 Communication with the IRB

4.1 Closure by the PI or Site Committee

If the PI or Site Committee decide to close the study to accrual either outside of PRMC review or as a result of PRMC's Request for PI Response, the PI should notify the IRB of record at the time of the next continuing review.

4.2 Closure by PRMC

If the PRMC Chair closes the study initially (and no appeal is received within 30 days), or the PRMC Chair denies an appeal, the PRMC informs the Director of Human Research Protection Program (HRPP) or designee of the closure AND the PI should notify the IRB of record at the time of the next continuing review.

The PI must notify the IRB of all study closures; if the PRMC's closure is not appealed or the appeal is denied, the PI should report the closure at the next continuing review.

Policy Exemptions

Alternate Procedure for Pediatric Malignancies

The Pediatric Oncology Site Committee completes their own annual assessment of accrual for all studies within their portfolio. The Pediatric Oncology Site Committee's responsibilities are to:

- Perform the review in the same month every year, and at least annually
- Select all protocols in its portfolio that are both Open to Accrual in the CTMS since the date of the last review and are *not* PRMC Exempt
- Either the Site Committee, or the Chair and at least one Co-Chair, must review scientific relevance and accrual goals versus the accrual to date, and determine whether the status of each protocol needs to change; the PRMC Chair or Vice Chair also attends this review
- Clearly record the recommended status for each protocol
- Ensure that all appropriate source data systems, including the CTMS, are updated in terms of both status and accrual data
- Provide the PRMC with a copy of the full review, signed by the Chair and at least one Co-Chair.

Policy Approval

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

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Clinical Research Policy Revision
Summary of Changes

Policy Title: PRMS Protocol Closure Policy
Version Date: 12/16/2024
Version Number: Revision 8

Section(s)	Summary of Change	Rationale
All	Policy reformatted to conform with the HDFCCC Policy on Clinical Research Policies.	Policy reformatted to match new requirements.
All	Editorial changes; added links/bookmarks; updated committee name from PRC to PRMC; replaced “OnCore” with “CTMS”; replaced “expiration” with “renewal”; changes to terminology, e.g., elimination of most usages of “patient” and “trial”.	To align with NCI guidelines and current HDFCCC practices.
Purpose	New section added.	Policy reformatted to match new requirements.
Scope	New section added.	Policy reformatted to match new requirements.
Definitions	New section added.	Policy reformatted to match new requirements.
Background	Updated to match language used elsewhere.	To align with other policies.
1.0	Clarified scope of SC reviews to reflect expectations on ensuring timely accruals and representation of underrepresented populations; clarified language on corrective action plans; removed specific timing of subsequent SC reviews	To reflect current expectations.
2.0	Clarified language on waiver requests; added language concerning ad hoc waivers.	To match current practice.
2.0	Removed notification to National Group Chair and institutional PI on National Group protocols.	Only Institutional PI need be notified.
2.0	Added reference to significant temporary closures (Suspensions)	To match current practice, as Suspensions are considered during PRMC review.

2.0	Added Departmental Reliance to Exceptions	Anticipating implementation of new review type.
2.0	Removed Deputy Director review of DT4, replaced with ad hoc DT4 reviews by PRMC Chair.	Shift in policy.
2.0	Added new exception to warning letters sent for zero accruals.	Shift in policy: studies with zero accruals and waiver but with annual accrual minimums above 1 may sometimes receive warning letters.
4.0	New section added to address all communications with IRBs; IRB-related language from other sections deleted.	To better identify the circumstances under which IRB notification is required.
Policy Exemptions	Updated Pediatric SC language.	To match current practice.
Policy Approval	Updated Signatories.	To match new requirements and changes in leadership.