



## **Protocol Review and Monitoring Committee**

### **Policies and Procedures**

**Effective February 2020**

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## 1 The Protocol Review and Monitoring Committee (PRMC)

A Protocol Review and Monitoring System (PRMS) is required for all National Cancer Institute (NCI)-designated Cancer Centers; the Protocol Review and Monitoring Committee (PRMC) serves in that capacity at Siteman Cancer Center (SCC). The PRMC fulfills the NCI expectation that all NCI-designated cancer centers scientifically evaluate and prioritize all cancer center trials derived and supported from institutional sources, including those originating from other cancer centers or from industry. The PRMC also provides a mechanism for monitoring all cancer research studies in the institution for scientific progress, carrying with it the authority for closing any studies that are not making sufficient scientific progress or meeting accrual or performance standards.

All initial submissions of cancer-related new studies being conducted at Washington University must be reviewed and approved by the PRMC prior to activation. Renewals and amendments are reviewed and approved independently. Due to limited scientific contribution, the following new projects do not require PRMC review: advertisements, case studies, and non-human subjects research determination requests.

The Director of SCC appoints members of the SCC research community to join the PRMC. The PRMC is composed of faculty members with diverse areas of expertise, including basic laboratory, clinical, prevention and cancer control, and population-based science. The committee also includes statistical, pharmacy, data management, and patient advocate reviewers to provide a critical and fair review of all clinical cancer protocols. PRMC members are asked to serve for two years and may be reappointed for additional terms. PRMC members are selected based on the experience they have in designing or conducting clinical trials or based on special clinical expertise (nursing, pharmacology, etc.).

## 2 Goals and Responsibilities of the SCC PRMC

The primary goal of the PRMC is to ensure that all cancer-related research studies involving human subjects conducted under the auspices of the SCC are (1) scientifically and statistically sound; (2) appropriately designed; (3) feasible for completion; and (4) if applicable, in compliance with National Institutes of Health (NIH) guidelines for clinical trials, including monitoring for accrual and undue toxicity. The PRMC is not intended to duplicate, or overlap with, the responsibilities of the IRB, nor is it intended to audit for quality control or safety reasons.

### Specific Responsibilities of the PRMC

The PRMC is responsible for:

- Providing scientific peer-review for all institutional and industry-initiated cancer research studies (with the exception of studies listed in Section 4.4, which undergo administrative review by a committee co-chair)
- Ensuring proper study design
- Reviewing all active cancer research studies for renewal/termination
- Reviewing accrual for all active cancer research trials

### 3 Definitions

For the purpose of this document, we define a clinical trial using the NIH's definition: a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it. [NOT-OD-15-015, 10/23/14; <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>]

The 2018 Common Rule definition of research is: a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge [45 CFR 46.102(1)].

The 2018 Common Rule definition of human subject is: a living individual about whom an investigator conducting research: (1) obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens OR (2) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens [45 CFR 46.102(e)(1)].

The term “prospectively assigned” refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial [NOT-OD-15-015, 10/23/14; <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>].

An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and diagnostic strategies [NOT-OD-15-015, 10/23/14; <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>].

Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and positive or negative changes to quality of life [NOT-OD-15-015, 10/23/14; <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>].

In the area of molecular or imaging diagnostics, the SCC considers a study to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. In this way the information from the diagnostic test may have an impact on some aspect of outcome, and assessment of this impact may be a key goal of the trial.

A behavioral trial is a study in which either (a) the intervention employs behavioral strategies, procedures, or theory, or (b) the primary outcomes involve behavior change on the part of patients, clinicians, families, or larger systems (e.g., change in worksite policies). Interventions may pertain to cancer prevention, early detection, treatment, and survivorship.

Observational studies and those that do not test interventions are not clinical trials (but do qualify for review).

“Cancer-related” studies are defined as studies that meet at least one of the following criteria:

1. The objectives of the study involve the diagnosis, prevention, screening, evaluation, treatment, or support of cancer patients.
2. At least 30% of the patients involved in the study are likely to have an active cancer diagnosis.

## **4 PRMC Policies and Procedures**

### **4.1 Protocol Prioritization**

NCI guidelines require that a mechanism be established within a cancer center for prioritizing competing research studies that may enroll subjects with similar eligibility criteria. At the SCC, all clinical trials must be evaluated and approved by the corresponding Clinical Focus Group before submission to the PRMC. Evidence of Clinical Focus Group evaluation and approval is provided by signature and comments (when appropriate) by a Clinical Focus Group leader on the “Request for Initial Review of a Protocol” form. Clinical Focus Group leaders review a list of active clinical trials (including patient eligibility criteria) to facilitate determining whether a new study will compete with/overlap with an existing study. If a research study is deemed to be in competition with an ongoing study, the Clinical Focus Group must determine whether SCC’s patient population can justify keeping both studies open for subject accrual or if any competing study or studies will need to be closed. When a Clinical Focus Group determines that it is acceptable to have competing studies open, it should establish a prioritization rule for subject accrual to those competing studies: in general, the highest priority should be given to institutional studies, followed by cooperative group studies, and then by industry-initiated studies. Clinical Focus Group leaders must provide clear rationale when there is more than one study for a specific population and prioritize the order in which studies are offered to patients.

### **4.2 PRMC Meetings**

PRMC meets three times each month to evaluate all newly submitted cancer-related research studies (as well as any existing studies referred to full committee). Meetings reviewing biomedical studies occur approximately every two weeks. Once a month, reviewers with specific expertise in behavioral research meet to review protocols that focus

on primary or secondary cancer prevention behaviors, quality of life in cancer patients, and epidemiological data related to cancer control, prevention, or incidence.

In order for a PRMC meeting to convene, quorum must be met. A quorum is defined as at least 50% of the number of full members for that particular meeting time and must include at least one co-chair and one statistical reviewer. Quorum may be met by full or ad hoc members. In addition to a quorum requirement for a meeting to convene, there is an individual attendance requirement for committee members: reviewers who attend fewer than 50% of scheduled meetings over the course of a year may be removed from the PRMC.

The PRMC has designed Protocol Evaluation Forms based on the NCI's Investigator Handbook to facilitate the review and committee discussion of each study; these forms are published on the PRMC website (<https://siteman.wustl.edu/research/clinical-research-resources/prmc-reviewer-forms/>). Principal investigators (PIs) are encouraged to review these documents to help them better understand the necessary components of a complete protocol and the criteria the PRMC will be using for protocol review.

### 4.3 Types of PRMC Review

There are two mechanisms for review by the PRMC: **administrative review** and **full-committee review**. The types of submissions that fall into these two categories and the procedures for their review are detailed below.

### 4.4 Submissions to Receive Administrative Review

- NCI-approved national cooperative group studies
- NCI Cancer Therapy Evaluation Program (CTEP)-approved and Division of Cancer Prevention (DCP)-approved studies
- Studies that have a peer-reviewed protocol supported by any of the various NIH mechanisms (e.g., R01s, U01s, U10s, P01s, P50s, etc.) and funding agencies (<https://cancercenters.cancer.gov/documents/PeerReviewFundingOrganizations508C.pdf>)
- Secondary institutional studies (investigator-initiated studies not written by an SCC investigator) with documentation of previous peer review and approval at an NCI-designated cancer center that is in good standing with the NCI
- Cancer studies that the PRMC co-chairs specify as not requiring scientific peer review. These include retrospective studies (chart reviews and existing specimen studies); compassionate-use protocols (only safety data being collected); studies that are not hypothesis-driven in which subject participation involves only prospective specimen and/or data collection; registry studies; and standard treatment protocols that are not designed to answer a scientific question or test a hypothesis but for which IRB review and approval is desired by the PI.
- Most study amendments/changes in protocols or risks of studies, with the exception of significant amendments/changes in protocols, including major changes to study design or risk/benefit ratio
- Annual renewal of cancer studies previously reviewed by the PRMC

#### 4.4.1 Administrative Review Procedures

**New Studies:** PIs will submit research studies that meet the requirements for administrative review to the SCC Protocol Office via the Clinical Trial Management System (CTMS) before IRB review begins. The submission should include:

- The completed Request for Initial Review of a Protocol Form (with Clinical Focus Group leader signature if the study is a clinical trial)
- The IRB application (may be a draft)
- The complete protocol with all appendices (if applicable)
- Model consent or draft consent (if applicable)
- The Investigator's Brochure (IB) and/or package insert(s) (if applicable)
- Documentation of prior scientific approval at an NCI-designated cancer center (if applicable)
- Documentation that the PRMS of the NCI-designated cancer center that provided prior scientific approval is in good standing with the NCI (if applicable)

The PRMC staff will verify that the study meets administrative review requirements. The study will then be reviewed by one of the PRMC co-chairs, who may determine that the submission would benefit from undergoing full committee review. For multi-site trials where SCC is not the coordinating center and the PRMC is conducting an administrative review after prior scientific approval at an NCI-designated cancer center, the co-chair's administrative review will focus on prioritization, competing studies, and feasibility at SCC. If the study is approved, the study team will be notified of the approval. A record of the PRMC review (including submitted materials) will remain on file in the SCC CTMS.

**Annual Renewals:** Each (non-IRB exempt) protocol is to be renewed through the PRMC until it meets both of the following criteria:

- Permanently closed to accrual
- All participants off active intervention with off-treatment dates entered in the CTMS as applicable

Once both of those criteria are met, the study should be closed with PRMC and no further reviews are required. "Active intervention" is defined in Section 3; participants in follow-up that includes study-mandated procedures will be considered off active intervention if the main study intervention has been concluded.

PIs are asked to submit their continuation review documentation (IRB application or proof of approval from external IRB) along with a completed PRMC Continuation Review Request Form at the time of IRB approval of the continuing review. For therapeutic institutional studies undergoing annual review, a copy of

the most recently approved Data and Safety Monitoring (DSM) report and annual quality assurance audit report most also be submitted.

The study team will be notified of the approval but may receive queries relating to accrual or study progress prior to release of approval.

***Amendments/Revisions:*** All protocol revisions are to be reviewed by the PRMC until the study is closed with PRMC, at which point no further reviews are required. A study may be closed with PRMC when it is permanently closed to accrual and all participants are off the main study intervention (refer to annual renewal section above). Whenever changes are made to a study, PIs are asked to submit redlined copies of the revised study documents (as applicable), a clearly delineated summary of changes with justification for the changes, IRB amendment application (for locally reviewed studies) or proof of external IRB approval (for externally reviewed studies), and a completed PRMC Change Review Request Form. Without a clear justification for the amendment, the submission will be returned for more information. The study team will be notified of the approval.

***Study Accrual:*** PRMC has ultimate oversight of accrual monitoring and study closure due to unsatisfactory accrual. Study accrual is monitored quarterly across SCC for active or suspended trials. At each quarter, studies that have had zero accrual over the past 6 months or more will receive a notification of zero accrual. No response is required.

In addition, study accrual is monitored at the time of continuation review. Studies that are at 25% or less of annual target accrual will be queried. After review of the justification for low accrual, consideration for extension of one year will be given.

If a PRMC co-chair determines that a formal closure to accrual is required, the notification of closure to accrual will be sent to the PI (and designee, if applicable). The PI (or designee) will be expected to submit the required closure documentation to PRMC and, when applicable, the IRB (with the understanding that closure to accrual does not always correspond to IRB closure).

In general, studies of rare cancers, cancers involving rare molecular subtypes, uncommon clinical subsets of more common cancers, and targeted therapies are excluded from this accrual monitoring process due to the importance of participation in multi-site trials of this nature.

#### **4.5 Studies to Receive Full-Committee Review**

- New institutional cancer research studies; this category includes institutional studies that did not undergo extramural peer review.
- New industry-initiated cancer research studies.
- Survey/questionnaire studies (unless deemed appropriate for administrative review by a co-chair).



- Significant amendments/changes in protocols, including major changes to study design or risk/benefit ratio.
- Any submissions referred from an administrative reviewer.

#### **4.5.1 Full-Committee Review Procedures**

All new studies that are received on or prior to the deadline will be placed on the agenda for the next committee meeting. The submission must include:

- The completed Request for Initial Review of a Protocol Form (with Clinical Focus Group leader signature if the study is a clinical trial)
- IRB application (may be a draft)
- The complete protocol with all appendices (research grant applications are not sufficient; see below)
- Draft or model consent form
- The Investigator's Brochure and Pharmacy Manual and/or package inserts (if applicable)
- Surveys/questionnaires (if applicable)
- Data collection forms or data dictionary (if the study is an institutional clinical trial)

Research grant applications (which are typically limited in page length) lack sufficient detail to allow for adequate review of the study by the PRMC. Accordingly, the submission to the PRMC for such studies should include a detailed study protocol in standard protocol format to facilitate PRMC review. PIs who have not previously submitted to the PRMC are strongly encouraged to seek assistance from the SCC Protocol Development group and Biostatistics Shared Resource.

In compliance with the Institutional Data and Safety Monitoring (DSM) Plan, each protocol must contain a study-specific DSM plan. The purpose of a DSM plan is to outline the procedures for review of study data for integrity, accuracy, and safety purposes. Specific requirements and suggested language are available in the Quality Assurance and Safety Monitoring Committee (QASMC) policies and procedures document available at:

<https://siteman.wustl.edu/research/clinical-research-resources/quality-assurance-and-safety-monitoring/>

Each study that receives full-committee review is reviewed by:

- a primary reviewer (typically a physician)
- a secondary reviewer (typically a physician)
- a biostatistician
- a pharmacist (if appropriate)
- a behavioral scientist (if appropriate)
- a nurse (if appropriate)
- a data manager (for Washington University [WU] and secondary institutional studies only)

- a patient advocate
- a representative from the SCC Protocol Development group (for WU institutional studies not submitted by that group)

Review assignments are made by the co-chairs to the individuals best qualified for review of each study. Conflicts of interest are taken into consideration when making reviewer assignments; any reviewers who are listed on the study team for a submission will not be assigned as a reviewer and will be asked to leave the room during voting. All review materials are posted in SCC's CTMS to which all PRMC members have access.

The primary reviewer is responsible for summarizing the merits and weaknesses of the study for presentation to the full committee. If the primary reviewer is unable to attend the meeting, the secondary reviewer or one of the co-chairs presents the study. For each study, the assigned reviewers each complete an electronic Protocol Evaluation Form specific to their field of review. In addition, the reviewers are encouraged to contact the PI before the meeting if there are questions regarding study design or other issues.

During committee discussion of a protocol for which a member of the PRMC is a member of the study team, that member may be present for the discussion or asked to leave the meeting for all or part of the discussion, at the discretion of the co-chairs. However, that member must leave the room during the vote. PIs are welcome to attend the PRMC meetings at which their studies are reviewed but are asked to leave the room during the final discussions and formal vote.

After full-committee discussion, the committee will make one of the following determinations:

1. *Approved or Approved with Comments.* A study that is approved with comments may warrant minor changes in the protocol, IRB application, or consent form. The committee recommends that the PI incorporate these suggested changes before the protocol submission is reviewed by the IRB.
2. *Contingent Approval.* A contingent approval includes comments requiring minor revisions or clarifying responses from PI. After one of the co-chairs of the meeting that originally reviewed the study approves the PI's response to the contingencies, the study team will be notified of the approval. The co-chairs also may request that one or more of original reviewers evaluate the adequacy of the PI's responses or may return the protocol back to the full committee for further evaluation and discussion of the changes.
3. *Deferred.* A deferral indicates that deficiencies were identified and substantial additional information or substantive revisions are required. After a response from the PI is received (along with updated study documents as necessary),

deferred studies must be re-reviewed by the full committee at the next monthly meeting of the same group that originally reviewed the study.

4. *Disapproval.* A disapproval indicates that major deficiencies were identified. To be reconsidered, a detailed response with either a revised protocol or additional supplemental information must be submitted and reviewed by the full committee.

A letter from the committee stating the determination is sent to the PI and study submitter, along with the reviewer comments.

#### **4.5.2 Response to Full-Committee Review**

For protocols that receive a contingent or deferred determination, PIs are expected to submit a response to the PRMC within 60 days. The response from the PI must be labeled with the PRMC number, address all concerns point by point, and include tracked changes versions of all revised documents. If no response is received within 45 days of the date of the letter to the PI, the SCC Protocol Office sends a reminder. If no response has been received at 60 days and no extension has been granted, the PRMC will close its file on the study. Written requests for extension of the 60-day response period will be considered on a case-by-case basis.

#### **4.6 Submission Work Instructions and Review Criteria**

Work instructions, forms, tools, and resources for both full committee and administrative submissions are published on the PRMC website:

<https://siteman.wustl.edu/research/clinical-research-resources/protocol-review-and-monitoring-committee/>

The criteria that are used by reviewers to assess scientific rationale, study design, potential duplication of studies elsewhere, expected accrual rates, biostatistical input, and feasibility for completion within a reasonable time period are also published on the PRMC website, as are the criteria used for monitoring ongoing institutional protocol research to evaluate scientific progress and accrual rates.

## **5 Quality Assurance and Safety Monitoring Committee**

The Quality Assurance and Safety Monitoring Committee (QASMC) functions to provide assurance that institutional studies are being conducted in accordance with the approved protocol and that data reported on clinical research forms accurately reflect the data as reported in the primary patient record. This committee reviews all institutional treatment studies and other studies designated by the PRMC (e.g., diagnostic trials). The PRMC will decide, at the time of initial approval, which institutional non-treatment research studies should be reviewed by the QASMC. Separate QASMC Guidelines are available on the SCC website:

<https://siteman.wustl.edu/research/clinical-research-resources/quality-assurance-and-safety-monitoring/>

## **6 Program for the Elimination of Cancer Disparities (PECaD)**

Ensuring appropriate representation by gender and race/ethnicity in cancer clinical trials is mandated by the NCI. All research with human subjects must include adequate numbers of women and minorities to allow for valid analyses of differences in the interventional effect; recruitment must be conducted so that no group is unduly burdened and that no group is unduly benefited; and any research proposal must describe the proposed study population in terms of gender and race/ethnicity as well as the rationale for inclusion.

The Program for the Elimination of Cancer Disparities (PECaD) monitors research accrual and supports investigators in their efforts to achieve appropriate representation.

Studies that are subject to PECaD review are: all interventional trials that are investigator-initiated (by WU investigators) regardless of sample size and any interventional trial for which the SCC target sample size is  $\geq 15$  subjects. The patient population at the Siteman Cancer Center for a given study's inclusion criteria is used as the standard for evaluation.

## **7 PRMC Co-Chair Responsibilities**

At least one of the committee co-chairs will sign the PRMC review letters from his/her committee meeting. In situations where both co-chairs are unable to sign (e.g. one co-chair is absent and the other has a conflict of interest), another senior reviewer will sign the relevant PRMC letters. At least one of the co-chairs will be present at each meeting. Each co-chair has the authority to approve all new studies that qualify for administrative review and studies resubmitted after receiving a Contingent Approval by the full committee. The co-chairs will determine if a study requires administrative versus full committee review and will check reviewer assignments for all full committee study reviews. Amendments also will be administratively approved, unless deemed by the co-chairs to represent a substantive change. Some amendment reviews may be approved by PRMC staff rather than a co-chair. Amendments representing substantive change will be brought to the full committee for review.

## 8 PRMC Review Process Flow Diagram

