PRMC Guidelines

Protocol Review and Monitoring Committee

University of Cincinnati Cancer Institute
09/11/2013
PRMC Guidelines

The PRMC provides a peer-review mechanism and strives to ensure that the clinical research at UCCI meets the highest standards of scientific merit, including appropriate study design, statistical methods, and feasibility of completion. This document provides guidelines for member roles and meeting conduct.

William Barrett, MD
Director, University of Cincinnati Cancer Institute
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PROTOCOL REVIEW AND MONITORING COMMITTEE GUIDELINES

OBJECTIVES:

All cancer related clinical research studies at the University of Cincinnati Cancer Institute [UCCI] are required to be reviewed and monitored by the Protocol Review and Monitoring Committee [PRMC] prior to submission to the Institutional Review Board of the University of Cincinnati. The PRMC provides a peer-review mechanism and strives to ensure that the clinical research at UCCI meets the highest standards of scientific merit, including appropriate study design, statistical methods, and feasibility of completion.

A. The Committee

The Chair of the PRMC Committee shall be appointed by the Director of UCCI. The PRMC Chair appoints the PRMC Rotation Subcommittee. Membership of the PRMC will be determined and reviewed on an annual basis by the PRMC Rotation Subcommittee. Members are selected based on their experience in designing or conducting research studies or special clinical expertise.

B. Responsibilities of PRMC Chair

The PRMC Chair will preside over the committee meetings to ensure consistent and fair proceedings and deliberations, and he/she will communicate with investigators regarding any outstanding issues from the protocol review so that the anonymity of the review is protected.

In the event that the Chair is unable to attend a meeting, he/she shall designate the Vice Chair or another full voting member to act on his/her behalf. In turn, an alternate voting member will serve on the committee in the place of the voting member.

C. Responsibilities of Committee

1. Review all new protocols involving cancer patients, cancer samples, or cancer patient records to ensure the highest quality of clinical research.

2. Continuing review of UCCI trials to monitor progress, maximize the scientific validity of research, and assure that enrollment goals are met.

3. Evaluate the merit of eligible protocols for utilization of UC Cancer Institute shared resources based upon objective scientific review.

4. Promote unified protocol implementation and translational research among investigators of various disciplines involved in cancer care.

5. Review justification for competing studies with similar patient eligibility criteria and implement prioritization plan. In general, the highest priority
should be given to investigator initiated trials (IIT), followed by cooperative
group studies, and then by industry sponsored studies.

6. The committee has the authority to approve protocols that meet the
scientific priorities of UCCI and close protocols that do not show satisfactory
progress or lack continuing scientific merit.

D. Membership

1. Comprehensive Membership List

<table>
<thead>
<tr>
<th>VOTING MEMBERS</th>
<th>Primary Members</th>
<th>Alternate Members</th>
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</thead>
<tbody>
<tr>
<td>Ad-Hoc members (as needed)</td>
<td>TBD</td>
<td>N/A</td>
</tr>
<tr>
<td>Basic Science</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Biostatistics</td>
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</tr>
<tr>
<td>College of Nursing</td>
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<tr>
<td>College of Pharmacy</td>
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<tr>
<td>Gynecological Oncology</td>
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<tr>
<td>Hematology/Oncology (Adult)</td>
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<tr>
<td>Otolaryngology</td>
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<tr>
<td>Pathology</td>
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<td>Radiation Oncology</td>
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<tr>
<td>Surgical Oncology</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
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<td><strong>12</strong></td>
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<thead>
<tr>
<th>NON-VOTING MEMBERS</th>
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<tbody>
<tr>
<td>Ex-Officio Members</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Rotating Members [CRCs]</td>
<td><strong>10</strong></td>
<td>N/A</td>
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2. Voting Members

- Voting members are expected to attend at least 8 out of 12 PRMC
  meetings in a calendar year with the designated alternate representing
  when a PRMC member is absent. The alternate member will have voting
  rights similar to the PRMC member they are representing.
- The Primary Reviewer is expected to present the study to the committee
  at the PRMC meeting. It is the responsibility of the primary member to
  communicate coverage needs to their alternate member and inform the
  PRMC Coordinator. Alternates are expected to present the assigned
  study review in the absence of the primary reviewer. The communication
  regarding absence should be conveyed by the primary reviewer to the
  alternate, secondary reviewer and the PRMC Coordinator.
- The **Secondary Reviewer** will present a brief review subsequent to the review presentation by the primary reviewer. The secondary reviewer may be expected to present the study to the PRMC in the event the primary reviewer is represented by an alternate reviewer.

3. **Ad Hoc Members**

- Represent those members of the UC Cancer Institute with a specific area of expertise. An ad hoc member will be invited to meetings to review sub-specialized protocols in their discipline on an ‘as needed’ basis. Ad hoc members will have voting rights similar to regular voting members.

4. **Ex-officio Members**

- The UCCI Director, UCCI Associate Director of Administration, and UC IRB Chair will serve as ex-officio members.

5. **Rotating Members**

- The Clinical Research Coordinators representing the disease areas of the protocols scheduled for review will attend the PRMC meeting as non-voting participants when feasible and provide input for consideration by the voting members. When attendance of the Clinical Research Coordinator is not feasible, he/she will provide the PRMC Administrator (UCCI CTO Director) with any concerns or comments for consideration in advance of the meeting. The number of non-voting members on PRMC roster may be limited at the discretion of the Chair.

6. **Non-voting Members**

- The PRMC Chair, PRMC Administrator, PRMC Coordinator, Ex-Officio and Rotating members will not have voting rights. The PRMC Chair will vote only in the event of a tie.

7. **Length of Term**

- For all voting members as well as the Chair and Vice Chair, a term shall consist of two to three years. There is no limitation to the number of terms one may serve.

8. **Committee Rotation**

- The PRMC Rotation Sub-Committee will meet once a year to review membership status and PRMC processes. New appointments, reappointments and revisions to the processes will be overseen by the sub-committee and executed by the PRMC Chair.
9. **Documentation**

- To ensure coordinated documentation and monitoring of UCCI research studies activities, the PRMC Coordinator will act as the single recording secretary for PRMC and the Data Safety Monitoring Board (DSMB). The recording secretary will be responsible for coordinating the meetings, recording the meeting minutes and facilitate communication between the committee members and investigators.

E. **PRMC Meetings:**

1. **Meeting conduct**

   - The PRMC will meet monthly, with 12 scheduled meetings in a calendar year.

   - The length of the PRMC meeting is 1.5 hours. If reviews are not completed within the time, the Chair may decide to complete the remaining reviews by email.
   - The Chair can also decide to hold protocols till the next regularly scheduled meeting.
   - At each meeting, all attempts will be made to complete the review of all the protocols on the agenda.
   - New protocols will be placed on the agenda in the following order: Investigator initiated trials have top priority, followed by industry sponsored studies and cooperative group studies.
   - CITI and FDA training status of the Principal Investigator [PI] is expected to be current and up-to-date for review of a protocol by PRMC.

F. **Types of Research Studies:**

   In addition to Investigator Initiated Trials (IIT), NCI Cooperative Group Trials and Industry sponsored studies, the PRMC also will review other types of Research Studies including the following:

   1. **Treatment protocols for Extension Studies**

      - These are protocols intended for treatment only and are commonly referred to as "treatment protocols," where the purpose of the protocol is simply to provide access to a standardized treatment plan. These protocols are presumed to not contribute to the scientific mission of the Cancer Institute and hence will not be scientifically reviewed by the PRMC. However, they will be viewed as competing trials for other scientifically reviewed protocols and hence will be reviewed by PRMC for local patient population with study diagnosis and accrual targets.
2. **Emergency Use**

- Emergency use is emergency clinical care and does not meet the DHHS definition of research.
- Emergency one-time use of a test agent (device, drug or biologic) is intended to benefit a single patient with a life-threatening condition who is not eligible for standard treatment or a study approved at the treating institution. Such use is allowed provided:
  
  - The test article is used one time to treat a single patient
  - The patient has a life-threatening condition
  - The patient is not eligible for standard treatment or an approved study
  - There is no sufficient time to obtain prior PRMC review and approval; in such instances, the PRMC will be notified within five working days after the emergency use and informed consent sought and documented
  - When possible, the treating physician will consult with the PRMC Chair or UCCI Director prior to use.

- A full protocol developed from this use will be reviewed at the next scheduled PRMC meeting, whereupon the protocol will be forwarded to the IRB.

- In the event that necessary treatment for a patient requires an emergency meeting of the IRB, this protocol should then be submitted after the fact for PRMC review at the next scheduled meeting.

3. **Compassionate Use (Expanded Access)**

- Compassionate use (also referred to as Expanded Access) is the use of an investigational drug outside of a clinical trial to treat a patient with serious condition when a comparable or satisfactory alternate treatment option is not available. PRMC review and approval is required prior to compassionate use treatment. The PRMC Fast Track Review process will be used for Compassionate Use studies.

4. **Innovative Treatment (Off-Label Use)**

- The innovative use of a marketed drug or device is also referred to as ‘off-label’ use. Such use for an individual patient treatment one-time does not require PRMC approval. However, if a series of patients are treated in this manner and the results analyzed for publication, it is considered research and requires prior PRMC and IRB approvals.
5. Significant Modification Request

- A significant Modification occurs when a study previously approved by the PRMC has a major amendment. A major amendment could be a change to the study design, inclusion/exclusion criteria, eligibility criteria, treatment, or analytic plan.

G. Administration of Research Studies

In keeping with these standards and the recommendations of the Institute of Medicine and per the requirement of UC IRB, the PRMC will conduct a scientific review of all cancer related non-exempt medical human research protocols prior to submission to the UC IRB.

PRMC will use 5 categories to process, review and record protocol research – (1) Fast Track Review, (2) Full Committee (3) Administrative Review, (3) Continuing Review (5) Ohio Clinical Trials Cooperative and (6) UCCI CTO Registration Process. Each is described as below.

1. Fast Track Review

- The review application will be submitted to UCCI CTO. The PRMC Chair and Administrator will determine when a study requires a Fast Track Review. The Fast Track review process is usually reserved for Phase I research studies but will include Compassionate Use and the Novartis Signature Program. The PRMC Chair selects the members of the Fast Track Review Committee.
- The study categories eligible for Fast Track review include:
  - Phase I research studies
  - Compassionate Use Protocols
  - Novartis Signature Program
  - Studies being submitted for funding to external grants agencies that require IRB approval prior to consideration. In this instance, the study will be approved by a Fast Track Review process, but not opened until funding has been secured by the investigator and reviewed by the UCCI CTO.
  - Surveys and Questionnaires

- Fast Track Review is typically conducted by Email. The email correspondence is initiated, tracked and managed by the PRMC Coordinator.
  - The Primary, Secondary, Biostatistician and Pharmacist reviewers will be required to complete the review via email.
- The PRMC Chair finalizes the vote with an emailed determination to the CTO and reviewers.
- Based on the reviews, the Chair may either approve the study or submit it to an administrative or full committee review.
- The PRMC Coordinator notifies the PI via email with a notification letter and manages/tracks any required response(s) until the study is approved, or disapproved.

- A Fast Track Review will typically be made within one to two weeks.

2. Full-Committee Review

- All protocols that require full, extensive review by the PRMC for scientific merit including appropriate study design, statistical methods, and feasibility for completion will undergo a full-committee review. All the required documents must be submitted by the PI to UCCI CTO by the PRMC submission deadline in order to be reviewed at the next scheduled PRMC meeting. The UCCI CTO will check for completion of criteria for review and forward the study packet to PRMC members for review.

3. Administrative Review

- Administrative Review will be conducted at the regularly scheduled PRMC meetings. While the documents required and review process will be similar to the Full-Committee Review, the main focus of Administrative Review will be to **analyze the study for possible overlap with existing open protocols** and to determine programmatic suitability. The review presentation of scientific merit by the primary reviewer will be brief compared to studies undergoing the Full Committee review process.

- Administrative Review eligibility. The study categories eligible for administrative review include:

  - NCI-approved national cooperative group studies
  - NCI Cancer Therapy Evaluation Program (CTEP)-approved studies
  - Division of Cancer Prevention (DCP)-approved studies
  - Other external peer reviewed studies if they were previously peer-reviewed and approved by NIH mechanism (e.g., P01, R01, U01, P50, etc)
  - Other peer-reviewed studies approved by agencies meeting NCI standard *(see list of NCI approved funding organizations in Appendix)*
  - Molecular or genetic epidemiology studies, observational and non-interventional studies (quality of life, and peer review).
  - Continuing Review of ongoing UCCI research studies
4. Continuing Review

- Continuing review of ongoing trials with initial administrative approval will focus on overall progress, accruals, resource utilization and continued scientific merit of the study.

5. Ohio Clinical Trials Cooperative (OCTC)

- The Ohio Clinical Trials Cooperative (OCTC) is a centralized scientific review (CSR) and Case Comprehensive Cancer Center (Case CCC) is the central Protocol Review and Monitoring Committee. The UC Cancer Institute is a participating member of the OCTC.
- As a participating institution, we will be asked to provide ad hoc reviews for research protocols being submitted to the OCTC and the Case CCC PRMC.
- The OCTC PRMC Manager will contact the UCCI CTO for review assignment. The UCCI CTO will distribute the review materials to the assigned PRMC member.
- Decisions form the CSR will be reported back to the UCCI CTO for recording purposes.

6. Registration Process

- A registration process only will be used to track categories that do not require committee review. An exception would be any unfunded study in the below category requesting CTO resources. The PI will submit a Registration Application to the UCCI CTO office.

This applies to the following categories. The PRMC Coordinator will notify the applicant when the study has been recorded.

- Collection of Blood Samples (Healthy +Non-Invasive Pts only)
- Biological Specimens (Healthy +Non-Invasive Pts only)
- Data (non-invasive)
- Retrospective Studies
- Medical Records

H. Review Process and Criteria

The investigator shall submit the following documents to the UCCI CTO for review of any new protocol. All submitted protocols must be in final format. No drafts or pre-finalized versions will be considered for review. A complete PRMC Submission Packet is required by the 15th of each month to be considered for the PRMC meeting. The PRMC Submission Packet from the PI should include the following (PDF Packet):
1. **PRMC Submission Packet**

   - A completed PRMC routing sheet is required with all protocol submissions. Any submission NOT including a completed routing sheet with original signatures will not be considered for review by the PRMC. Stamped signature will not be accepted. A submission packet consists of the following:
     
     - Routing Sheet (Completed).
     - Protocol and appendices.
     - Investigator Brochure, if applicable.

2. **PRMC Review Packet**

   - The PRMC Review Packet from the PRMC Coordinator to the reviewers should include the following (PDF Packet):
     
     - Routing Sheet (Completed).
     - Protocol and appendixes
     - Investigator Brochure, if applicable.
     - Protocol Score Sheet

3. **Protocol Score Sheet**

   - Protocols undergoing Full Committee review and Administrative review will be required to include a completed and signed Protocol Review Worksheet in the Protocol Review Packet. Primary, Secondary, Biostatistician and Pharmacist reviewers be assigned to each study will complete and sign the Protocol Review Worksheet requiring an evaluation/scoring of criteria.

   - Each protocol will be reviewed for the following criteria. The criteria with **asterisk** will require a score on a scale of 1-3

     1. Scientific rationale*
     2. Study design*
     3a. Primary End Points
     3b. Secondary End Points
     4a. Inclusion Criteria
     4b. Exclusion Criteria
     5. Expected Accrual*
     6. Adequacy of Biostatistics*
     7. Feasibility for completion within a reasonable time period*
     8. Scientific Impact*
     9. Funding
     10. Competing Trials
     11. Comments
- The six categories/criteria marked with an asterisk (*) will be scored using the following scale:

\[
3 = \text{Outstanding};\quad 2 = \text{Acceptable};\quad 1 = \text{Not Acceptable}
\]

Any protocol receiving a score of 1 for any category/criteria will not be approved. Therefore, totaling all 6 categories for a maximum score of 18, the protocol must score at least 12 points to receive approval.

- The investigator may attend the PRMC meeting during the discussion of his/her protocol, but cannot be present during deliberation and voting. The same applies when the PI of a study under review is a member of the Committee. A majority vote rules.

- Each investigator will be notified of the outcome of his/her protocol review within a reasonable timeframe, typically within 3 working days, in order to allow for corrections to be made prior to the IRB deadline. Specific criticisms or questions will be detailed in the written report forwarded to the investigator.

I. **IIT Fiscal review:**

Investigator Initiated research protocols will utilize the full committee review process keeping in mind the following guidelines.

- All IITs will require a budget listing each cost item and the funding source(s) for review by UCCI CTO to ensure feasibility and completion of the study.

- The University of Cincinnati Cancer Institute provides a Data Safety Monitoring Board for treatment trials that require a data safety monitoring board as part of their data safety monitoring plan. Monitoring by the UCCI DSMB will commence 6 months after the studies first accrual. Unless there is a significant safety risk or unique circumstance related to a specific trial. In this case, the PRMC chair has chair discretion. In some cases, it may be determined that the data forms will be distributed to the DSMB for review prior to the IRB Submission. Please contact your UCCI Clinical Trials Office for additional information regarding the DSMB Charter.

J. **Review Decisions:**

After review of a Research Study, the PRMC will make one of the following decisions:

1. **Approved** - A study may be approved (a) as submitted or (b) with specific and minor corrections as requested by the committee. The document(s) will subsequently be forwarded to the IRB.
2. **Approved with Contingencies**

- A study may receive provisional approval pending clarification or specific changes as indicated.

- If a study is approved with contingencies by the PRMC, it is the responsibility of the assigned reviewers to review the contingency response to determine if the contingencies have been met and determine the study approved.

- The PRMC Coordinator will generate a notification letter and send via email to the PI, notifying the PI of the required response.

- The PI has 6 months to send the contingency response to the CTO; if the contingency response is not received within 6 months, the study can be administratively closed.

- Upon receipt of the contingency response, the PRMC Coordinator will initiate the review by email and send to the assigned reviewers.

- The contingency response is reviewed by email and reviewed by the previously assigned Primary, Secondary, biostatistician, and pharmacist reviewers.

- The PRMC Coordinator tracks and manages the email correspondence and voting process.

- The Chair finalizes the vote with an emailed determination to the CTO and reviewers.

- Subsequently, the PRMC Coordinator notifies the PI via email with a notification letter and manages/tracks any required responses.

- An approved study will be forwarded to the UC IRB. If the contingency response is not acceptable to the reviewers, the study may require a full committee review by PRMC for further evaluation and discussion of the changes.

3. **Tabled**

- A study may be tabled pending significant scientific and/or regulatory revisions. Such studies will require a Full Committee review by PRMC when resubmitted.

- Studies may be tabled by the PRMC for the following reasons:
• Studies that do not meet the minimum requirement including patient safety and confidentiality as put forth by the University of Cincinnati Institutional Review Board (UC IRB)

• Inadequate or lack of information in the "Background" section of the protocol to justify the conduct of the trial.

• The protocol not meeting the study objectives including inadequate biostatistical design, faulty study design, or an improper/inadequate data collection design.

• Lack access to an adequate patient population to complete the trial in a reasonable time period. In general this will require that the investigator be an active participant in the multidisciplinary clinic for the disease to be studied, or submit a letter from the director(s) of the clinic assuring their active participation.

• If a competing study will require written justification and prioritization plan for consideration by the PRMC.

• It is a goal to achieve optimal resource utilization. If the Committee determines that a proposed study will consume an inordinate amount of resources either in terms of funds or personnel, the investigator will be asked to provide written justification for the use of these resources or resubmit the study after funding source(s) have been identified to cover the costs of the study.

4. Disapproved

- A study may be disapproved with specific reasoning provided via written communication. This protocol will not be eligible for usage of shared resources. The PI may address the PRMC comments and/or appeal via a letter to the PRMC. It is the Chairs discretion to consider re-submission.

K. Continuing Review

Each ongoing UCCI clinical research study must be reviewed at least annually for renewal. The first continuing review will be conducted at the one year anniversary of the study open to accrual date. The committee reserves the option to request review of a protocol on a more frequent than annual basis based on the study progress at the first review. The UCCI CTO will prepare a Continuing Review Routing Sheet, to be reviewed and signed by the PI for submission to the PRMC. The latest IRB progress report providing extensive information regarding the status of the study will be provided for all protocols.
All continuing reviews will be conducted by the PRMC using the Administrative Review process described earlier in the guidelines. The continuing review will focus on overall progress, accruals, resource utilization and continued scientific merit of the study. By a majority vote, a decision will be made to re-approve for one year, 6 months, or terminate the study. In rare instances, the PRMC may decide to renew the protocol for a period of 3 months.

Any study with accrual <50% of target/year will be required to provide an action plan to reach the expected target in the next review period in order to approve continuing renewal.

L. **Suspension or Termination of a Clinical Research Study**

Upon majority vote, the PRMC may suspend or terminate a clinical research study for reasons including, but not limited to, the following:

1. Insufficient accrual rate (following adequate notice and discussion with the PI)
2. Poor study performance (following adequate notice and discussion with the PI)
3. Patient safety concerns
4. Emergence of new information which diminishes the scientific merit of the study relevance

As outlined in the PRMC Routing Sheet, protocols submitted to the PRMC must provide information on local patient population with the study diagnosis and expected accrual target for the new trial. Accrual goals, competing trials, and track record of the investigators in successfully accruing to research studies will be taken into consideration in the evaluation of the overall feasibility of the research study.

**Research Studies (excluding cooperative group studies) which are expected to accrue a significantly low numbers of patients will be assessed critically for overall scientific value and feasibility of accrual.** It should be recognized that in instances where an over-riding reason for approval does not exist, disapproval of such studies will be considered. Such studies, if approved, will be subject to careful evaluation of accrual at the time of their continuing review.

A study should meet 50% of annual accrual goal to stay open for 12 months. If a study doesn't meet 50% of the annual accrual goal but is screening, then accrual goals should be reviewed and adjusted as directed by the committee. Other areas to consider for low accrual is patient population, PI participation, internal processes, extenuating circumstances, study specific inherent issues. A PI action plan will be required. The study will be approved for 6 months with a PI action plan. If accrual or screening has not improved, the study will be administratively closed.

M. **Relationship with UC Institutional Review Board**

The UCCI Protocol Review and Monitoring Committee functions independently of the University of Cincinnati IRB, and is considered to have a distinct role. The
primary charge of the UC IRB is to ensure patient safety, while the primary role of the PRMC is to maximize the scientific quality of research and the utilization of shared resources. Protocol Review Notification Letters, along with the study specific PRMC minutes, are forwarded to the IRB per their request.

N. Appendices

Appendix 1: Current year's PRMC meeting dates & deadlines
Appendix 2: PRMC Membership List
Appendix 3: PRMC Rotation Sub-committee List
Appendix 4: PRMC Review Process Flowchart
Appendix 5: PRMC Routing Sheet
Appendix 6: Continuing Review Routing Sheet
Appendix 7: Significant Modification Request
Appendix 8: Protocol Review Score Sheet
Appendix 9: PRMC Review Types
Appendix 10: List of NCI Approved Funding Organizations (click link to view)