PROTOCOL REVIEW COMMITTEE

Protocol Review and Monitoring System (PRMS)
Protocol Review Committee (PRC) Policies & Procedures

1 Definitions

CCSG	Cancer Center Support Grant
CRLC	Clinical Research Leadership Committee
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
IRB	Institutional Review Board
NCI	National Cancer Institute
PI	Principal Investigator
PRC	Protocol Review Committee
PRMS	Protocol Review and Monitoring System
UI Cancer Center	University of Illinois Cancer Center

2 Introduction

The PRMS responsibilities required for the CCSG are primarily carried out by the UI Cancer Center's PRC. The purpose of this policy is to document the review processes undertaken by the PRC.

The PRC evaluates all clinical research studies undertaken at the University of Illinois at Chicago involving patients with cancer or individuals at risk for cancer. The committee is responsible for:

- Undertaking scientific review of all new studies
- Assessing general feasibility, annual accrual expectations, and competing studies
- Assigning risk according to the UI Cancer Center's DSMP and informing the UI Cancer Center DSMC
- Reviewing all protocol amendments that affect study design
- Maintaining written records of all meetings
- Monitoring accrual and ongoing scientific relevance for all studies
- Requesting corrective action plans for poorly accruing studies and closing studies that do not meet accrual expectations

3 Procedures

3.1 New Studies

All research studies conducted at University of Illinois at Chicago involving patients with cancer or individuals at risk for cancer must be submitted to PRC and approved prior to submission to the IRB. All new study applications are reviewed by PRC Personnel to determine what level of review is appropriate. Studies may receive full committee or expedited review or be deemed exempt from PRC review.

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New Study Submissions

For new studies, the PI or Submitter creates a new study record via the ePRMS submission console using the OnCore Clinical Trials Management System (CTMS). In addition, the following documents must be uploaded to the record.

- Final Protocol
- Disease Team Feasibility Minutes or Clinical Trials Office Medical Director Feasibility Approval
- PI NIH Biosketch, if NIH Biosketch is not available a curriculum vitae (CV) may be substituted
- Protocol Supporting Documentation, this includes but is not restricted to: Scientific Approval Letter from designated site, Surveys, Questionnaires, etc.

Please note that prospective, hypothesis-driven, non-interventional studies (e.g., observational, ancillary, or correlative studies) do not require disease Team Feasibility Minutes or Clinical Trials Office Medical Director Feasibility Approval.

Levels of Reviews and Process

Expedited Review

Expedited Review typically includes:

1. NCI-approved cooperative group studies (National Clinical Trials Network) and NCI Cancer Therapy Evaluation Program (CTEP)-approved studies.

2. Other investigator-initiated studies that have or will receive external peer-review and funding by an approved NIH peer-review funding organization prior to activation. Extramurally funded studies that do not include a protocol as part of the peer-review process may, at the PRC Co-Chair's discretion, undergo a Full Committee Review.

3. Multi-site institutional trials previously approved by a PRMS from another NCI-designated Cancer Center. Documentation of the external PRC approval must be on file with the UICC PRC.

4. Prospective, hypothesis-driven, non-interventional studies (e.g., observational, ancillary, or correlative studies).

For studies meeting the expedited review criteria listed above, the PRC Co-Chairs should review all submission materials and give a rapid expedited review, assuring that conflicts with current studies do not exist, resources appear appropriate to implement and complete the study, and that appropriate data and safety monitoring and recruitment plans are in place. If no substantive issues are identified during the Chair's review, PRC Personnel will then generate an approval letter that is emailed to the Principal Investigator. In the event a conflict of interest exists and/or the Co-Chair is involved in the study being reviewed, the other Co-Chair will conduct the review and vice versa. Expedited reviews are typically communicated within ten business days of receipt. A summary report of all studies that received expedited review since the last PRC Full Committee is included in the agenda and noted in the minutes.

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Process for Protocols Included in Grant Submissions to Extramural, Peer Reviewing Agencies

If a grant submission has already been reviewed and approved for funding by a peer reviewing agency, an expedited approval letter from the committee will be issued to the PI provided the clinical trial has all of the required protocol elements.

If a grant submission has not been approved for funding by a peer reviewing agency (grant is pending review) but the investigator needs to seek IRB approval, a letter will be issued to the PI which will state that the trial is granted an expedited approval by the PRC contingent upon funding by the granting agency and approval by the IRB. If the trial is ultimately not funded by the granting agency and the PI wishes to proceed, the trial must be reviewed and approved by the full committee prior to being activated. This requirement will also be stated in the letter to the PI.

Exemptions

The following types of studies may receive PRC exemption and will not be included in CCSG Data Table 4.

- Retrospective chart review studies
- Institutional registries, databases, and serum and tissue banking protocols where there are no research hypotheses
- Single subject compassionate use or emergency use protocols where there are no research hypotheses

PRC Submissions for NIH JIT Requests

If a submission to the IRB is in response to an NIH Just In Time (JIT) request, all of the required documents and processes for both PRC and IRB review are required.

If the JIT submission is for a Core/Center grant, a Training grant, or a grant in which the human subject involvement will depend on the development or completion of instruments, procedures, or prior non-human studies, as defined by the IRB, the PRC will not review the application. A letter will be issued to the PI which will state that the submission is granted exemption by the PRC. However, if at any time the activities described in the submission involve human subjects, use of identifiable subject information, and/or pilot testing of instruments or procedures, the human subjects activities must be reviewed and approved by the full committee prior to receiving approval by the IRB.

Full Review

Studies that do not meet criteria for expedited review or exemption will receive full committee review.

Studies eligible for full committee review typically include the following:

1. Investigator-initiated studies: These generally are studies developed by UI Cancer Center faculty with funding from the institution, a non–peer-reviewing agency, or industry. Multi-institutional investigator-initiated studies where the study Principal Investigator is at another non–NCI-designated institution and the study has not undergone formal peer

review (as outlined in the Expedited Review criteria above) also require full committee review.

2. Industry-initiated studies: In these studies, the concept and protocol originate with industry.

Full committee review focuses on the scientific merit of the study, prioritization of the study within the larger portfolio, competing studies, and accrual feasibility. Committee members will address all scientific aspects of a proposed study according to defined review criteria, including but not limited to:

- The study addresses a relevant scientific question
- The primary and secondary objectives are scientifically sound
- The study design is appropriate to meet the objectives
- The response criteria and endpoints are clearly defined
- The sample size is appropriate to answer the question, accrual goals are clearly stated and the patient population is sufficient to meet accrual goals
- The data and safety monitoring plan is appropriate
- The early stopping rules are adequate and clearly described
- The investigator has an appropriate plan for the inclusion of women and minorities

Reviewers will also assign a level of risk to Investigator Initiated studies which will determine the recommended level of auditing and monitoring of the DSMC.

Determination of Risk

Each UI Cancer Center investigator-initiated study undergoes scientific review by the PRC, in part to ensure that procedures are in place to ensure the safety of subjects depending on the degree of risk of the study. The PRC assigns a category of risk to every UI Cancer Center investigator-initiated study and the DSMC follows the plan of review for that category.

The purpose of assigning a level of risk (low, moderate, or high) to an UI Cancer Center investigator-initiated trial is to ensure that data and safety monitoring activities are appropriate for the level of subject risk. In order to make a decision, the PRC reviews the following criteria:

- Expected duration of the study based on the study design and estimated rate of enrollment.
- Study population (e.g. children, pregnant women).
- Procedures to ensure the safety of subjects in accordance with the degree of risk.
- Methods to ensure the validity and integrity of the data, including adequate biostatistical design and appropriate data analysis.
- Adequate data management systems including case report form records and a plan for data collection.
- Procedures for reporting serious adverse events to the appropriate departments/committees (e.g. IRB, FDA, NIH).

The risk level determines the frequency of monitoring for a protocol, which may be altered (i.e., increased) as and if issues arise.

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Definition of Risk Levels

There are three levels of risk that may be assigned: High, Moderate and Low. Each category is described below. Please reference the UI Cancer Center's DSMP for monitoring frequency based on risk assignment.

High Risk
Studies assigned to the high-risk category include any therapeutic investigator-initiated Pilot, Phase I, II, or trials involving IND/IDEs, investigator-initiated multi-center trials and any research involving recombinant DNA molecules (gene transfer).

Moderate Risk
Studies assigned to the moderate-risk category include most investigator-initiated Phase I or II trials using FDA-approved.
Low Risk
Studies assigned to the low-risk category include investigator initiated phase III and non-therapeutic trials.

Protocol Review and Response Expectations

Study submissions that have been received 13 BUSINESS days prior to the scheduled PRC meeting will be assigned to a minimum of 3 reviewers by the PRC Co-Chairs. Studies submitted after 13 business days will be assigned to the next scheduled PRC meeting.

- For treatment studies two reviewers **must be** treating physicians, and the third reviewer must be a statistician. Additional reviewers may be assigned as appropriate.
- For non-treatment studies, two researchers with relevant expertise may be assigned as reviewers.

Reviewers are required to complete PRC review forms (accessed in OnCore) prior to the PRC meeting in order for the protocol to be discussed and voted on at the meeting. If review forms are not completed prior to the meeting, the protocol may be tabled until the next PRC meeting, at the Co-Chair's discretion.

The PRC review outcome will be emailed to the PI and the Submitter no later than ten business days following a meeting with an electronic copy of a signed letter containing a summary of the committee's deliberation and comments if applicable. Please note that after receiving the PRC decision letter the PI should provide a response within 15 business days for a "modifications required" outcome and within 30 business days for a "deferred" outcome. If no response is received, the study will be disapproved.

New Study Review Outcomes

Once the new study review is completed, the PRC personnel will prepare a review outcome notification that will be issued to the PI and Submitter. Review outcomes include the following:

- Approved
    - The study is approved for activation as submitted and may proceed to the IRB. The PI and Submitter will receive an approval letter.
- Modification Required

  - The study review results in concerns that require a PI response which may include minor modifications to the study or study materials. PI and Submitter will receive a letter requesting a written response to the concerns. Should the response be found to be satisfactory, as determined by the PRC Co-Chair or the original reviewers, the PI and Submitter will receive a final approval letter.
  - If the PI does not respond within 15 days of receiving PRC decision letter, the study will be disapproved at the discretion of the PRC Co-Chair.
- Deferred
  - Significant revisions to the study are necessary. PI will receive a letter requesting a written response to the concerns, and the study must be re-submitted and re-reviewed at a full committee meeting. If all concerns are addressed, the PI and Submitter will receive a final approval letter.
  - If the PI does not respond to the PRC within 30 days of receiving a PRC decision letter, the study will be disapproved at the discretion of the PRC Co-Chair.
- Disapproved
  - The study does not satisfy the review criteria and is not approved for activation. The PI and Submitter will receive a disapproval letter.

3.2 Annual Continuation Review and Accrual Monitoring

Annual Continuation Review

Evaluation of the scientific progress of studies and how they fit into overall progress in their specific area of research is important to ensure that the study is continuing to address an important scientific question.

Studies are reviewed annually from the date of PRC approval, however the PI and/or Submitter can request to reset the annual review date to one year post IRB approval.

The purpose of the annual progress review is to:

1. Evaluate major developments that occurred in the scientific area that affect the specific objectives of the study
2. Determine if sufficient progress is being made, including accrual
3. Monitor changes in the study's priority
4. Summarize any interim analysis and any significant study outcomes (e.g. met DLT, met accrual on specific study arm)

Annual Continuation Review Submissions

For all annual continuation review submissions, PI or Submitter creates a continuation record via the ePRMS submission console using the OnCore CTMS.
Submission requirements:

- PRC Annual Continuation Review Form, please note all fields are required
- Current protocol

The annual continuation review submission must be submitted to PRC prior to PRC expiration each year until the study is permanently closed to accrual.

Annual Progress Review Process

Annual continuation review submissions are reviewed by the PRC Co-Chairs. PRC Personnel will review each annual continuation review submission for completion and once complete, forward it to the PRC Co-Chairs for review via an expedited review process. The PRC Co-Chairs have the prerogative to refer any annual continuation review submission for full committee review.

Accrual Monitoring is an integral part of the annual continuation review process and must follow the guidelines as outlined in section 3.3.

Annual Continuation Review Outcomes

After review by the PRC Co-Chairs, PRC Personnel will either prepare a review outcome notification (approved for continuation or disapproved for continuation), or prepare the submission for full committee review, depending on the outcome. Review outcome notifications are issued to the PI and Submitter.

When a PI closes or terminates a protocol, the status must be updated in OnCore and an electronic communication should be sent to PRC Personnel stating that the research is no longer ongoing. A continuing review is no longer required when a study has been closed to accrual.

3.3 Accrual Monitoring

Accrual monitoring will be conducted for all active interventional studies semiannually. Prior to the accrual monitoring meeting, PRC Personnel will run a report identifying the status of all studies and their accrual. PRC Personnel will send out requests for justification of continuance to the PI of studies not meeting expected annual target goals (see below). The PI will be given 15 business days to respond. The PRC Co-Chairs will then review PI responses at their quarterly PRC meeting and determine if the study should remain open.

Target Accrual Reporting

At the time of initial PRC submission, the investigator is required to project the estimated total accrual and the estimated total duration of the study accrual. These projections will be utilized by the PRC for monitoring accrual progress

Quarterly, PRC Personnel generate a report identifying prospective interventional oncology studies that are actively enrolling cancer patients/subjects with the following fields:

- Protocol Number
- PI name
- Study title
- Indication if the study is targeted for a rare cancer and/or is a molecular targeted therapy
- Date the study was opened to accrual
- Any temporary suspension and re-open dates
- Research Center's (RC) anticipated (lower) target accrual
- RC anticipated duration for accrual
- RC total actual accrual to date

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- **Percent Accrued** = RC total actual accrual / RC anticipated (lower) target accrual

- **Percent Duration Completed** = [Number of months expired] - [Number of months suspended] / RC Anticipated Study Duration (in months)

- **Percent Accrued to Date** = "Percent Accrued" / "Percent Duration Completed"

For those studies where the *Percent Accrued to Date* falls below 50% of the projected annual accrual, PRC Personnel will issue a written notification requesting a response or justification from the PI. The PI shall be given 15 business days to respond to the notice with a specific plan to increase accrual. The PI's response will be reported to the PRC Co-Chairs approximately one month following the report's generation. The PRC Co-Chairs will determine if the PI's response is acceptable and whether the study may continue as planned, requires further justification or additional information, or will be closed to accrual.

During the review period, PRC Personnel will also monitor those studies that have attained or exceeded their accrual goals. PRC Personnel will send a notice of acknowledgment to the PI that accrual monitoring has occurred and accrual goals have been met. For studies that have exceeded their goals, the PI will be advised to consider whether a modification request to applicable study sponsors and the IRB is warranted to increase accrual goals. Modifications in accrual goals must be reported and approved to the PRC.

Table 1. Summary of PRC Accrual Expectations and Action Guidelines

Study Accrual Status	Type of PRC Accrual Monitoring Review	PRC Actions
All Prospective Interventional Studies Involving Rare Cancers and Molecular targeted therapies	Annually	Approved for continuation if scientific aims remain relevant. Justification of continuation of studies with ≤1 accrual per year is required.
Interventional Studies opened < six months	Exempt	N/A
Interventional Studies opened > six months	*All Studies with the following accrual status are subject to PRC Accrual Review.* *See categories below for expected PRC actions*	

Percent Accrued to Date ≥ 50%	Semiannually	Approved for continuation
Percent Accrued to Date < 50%	Semiannually	1st Review: Contingently Approved. The PI will be informed that accrual will be closely monitored during the next quarter and if sufficient progress is not made, the PI will need to provide more justification and/or a revised corrective action plan. 2nd Review Should the PI either: - fail to provide a corrective action plan, *and/or* - fail to improve accrual, *and/or* - fail to demonstrate adequate screening activity then the PRC will require the PI to close the study. Should the PI: - Provide a corrective action response and/or demonstrate an improvement in the accrual and/or screening activities the accrual review may be approved. Decision to close study: PI will be requested to provide study closure documentation (communication with IRB and/or Sponsor).

3.4 Protocol Amendments

Protocol amendments for studies that have been reviewed by the full committee and affect the principal elements of the original protocol, including but not limited to: study rationale, response criteria, eligibility criteria, objectives, study design, treatment plan, sample size, stopping rules, or statistical plan, must be submitted to the PRC in concurrence with the IRB for review and approval. Amendments that do not impact the aforementioned areas do not require PRC approval.

Amendment Submissions

For all amendment submissions, PI or Submitter creates a change review record via the ePRMS submission console using the OnCore CTMS.
Submission requirements include:

- PRC Amendment Committee Amendment Review Form with summary and justification of changes
- Clean, revised protocol

Amendment Review Process

PRC Personnel will review each amendment submission for completion and once complete, assign it to the PRC-Chairs for review. The PRC Co-Chairs have the prerogative to defer any amendment for full committee review.

Amendment Review Outcomes

After review by the PRC Co-Chairs, PRC Personnel will either prepare a review outcome notification, or prepare the submission for full committee review, depending on the outcome. Review outcomes include, approval, modifications required or disapproval. A review outcome notification of "approval" is issued to the PI and Submitter. A review outcome notification of "modifications required" will include an explanation of which revisions were not acceptable and why, and may contain suggestions as to how the PI can make the revisions acceptable.

PRC Membership and Meeting Organization

Meetings

The PRC meets twice each month, the second and fourth Thursday of every month at 4pm CT. Cancellations or modifications may be allowed for holidays and other unforeseen circumstances and will be communicated center-wide. Meetings may be recorded to assist with minutes and documentation.

Member Anonymity

The identity of the PRC members reviewing a particular trial will remain anonymous to the submitter of the protocol and to the general UI Cancer Center community. If the submitting PI has questions or concerns about PRC comments, they are asked to submit these questions to the PRC Personnel who will reach out to the appropriate committee member for clarification. PRC Personnel will respond to the PI without revealing the identity of the reviewers.

Conflicts of Interest

A PRC member who is the PI or Co-Investigator of a study being reviewed at a PRC meeting is recused from the meeting during the review, discussion, and voting on the protocol.

PRC Membership

PRC membership will include broad representation across medical disciplines in order to provide the highest quality study reviews. The Cancer Center Director and the Associate Director of Clinical Research shall identify and appoint established researchers as Co-Chairs of the PRC, ideally two senior faculty representing different disciplines. Potential PRC members are identified by the Associate Director of Clinical Research and the PRC Co-Chairs and presented for review and

approval by the Cancer Center Director. The PRC must consist of members with active membership with the Cancer Center. The PRC must include representation from biostatistics. The PRC must be comprised of 60% senior faculty (full professor and associate professor). Junior faculty may be appointed but must meet minimum experience criteria including: 3 years post fellowship completion, enrolling 5 to 10 patients to study per year, experience as PI through completion of at least 1 study, and publications on research study outcomes.

PRC membership shall be a three year commitment with a two term maximum. Members are expected to attend 75% of meetings annually or membership may be revoked at the Co-Chair's discretion.

Members of the PRC may not serve simultaneously on the DSMC, or as the Clinical Trials Medical Director or the Associate Director of Clinical Research. Members may serve on the IRB but must abstain from reviewing cancer research studies.

Initial and Ongoing Training

Quorum

Meeting quorum is 50% of committee membership and must include one of the PRC Co-Chairs and one biostatistician member.

Responsible Personnel

The Associate Director of Clinical Research, PRC Co-Chairs, and PRC Personnel are responsible for the execution of these policies and procedures. The PRC Co-Chairs report directly to the Associate Director of Clinical Research.

PRC Appeal Process

PIs can appeal any PRC decision by submitting a written request for an additional review to the PRC. However there is no appeal process beyond the PRC and the final PRC decision cannot be overturned. The protocol may be resubmitted at another time as a new protocol, provided there are substantial changes and/or modifications.