University of Virginia Cancer Center

Protocol Review Committee (PRC) Operations Manual

April 2012

Abbreviations

AE	Adverse Event
CCSG	Cancer Center Support Grant
CRC	Clinical Research Coordinator
CTEP	Cancer Therapy Evaluation Program
DSMP	Data Safety Monitoring Plan
IRB	Institutional Review Board
NCI	National Cancer Institute
PAM	Post Award Monitoring
PRC	Protocol Review Committee
PRMS	Protocol Review & Monitoring System
SOP	

The sponsor's protocol standalone protocol document that contains all of the information needed to conduct the protocol.

IRB protocol: In some cases PI will use protocol builder in IRB database to create main protocol document

IRB Application: The IRB application is created through protocol builder and contains all of the required elements of the DSMP for both the IRB and PRC.

Table of Contents:

I. Overview of PRC Purpose & Operation

What is the PRC?

The Protocol Review Committee, or PRC, is the institutional peer-review system for all cancer-related research. The PRC is charged with providing institutional peer-review of the scientific merit of all cancer-related clinical research protocols.

The PRC is the name of our local PRMS or Protocol Review and Monitoring System, which is the term that the NCI uses to refer to the body that performs the same function at every National Cancer Institute (NCI)-designated Cancer Center.

The primary goal of the PRC is to ensure that cancer-related studies involving human subjects conducted at the UVaCC are:

1) Scientifically and statistically sound;
2) Appropriately designed;
3) Feasible for completion; and
4) In compliance with NIH guidelines for human studies.

As part of the review process, the PRC:

- Reviews and approves protocol-specific data and safety monitoring plans on cancer-related trials prior to protocol review by the University of Virginia IRB-HSR.

- Reviews if a protocol competes with existing or pending protocols for a particular subject pool. The PRC does not approve protocols that directly compete with an open or pending institutional or NCI-sponsored trial

Why is the PRC review required?

Each NCI-designated Cancer Center is required to have a PRMS, and other committees to help regulate and report on the research being done at the Cancer Center.

This Manual is created by using directives from the NCI, UVa Institutional Data and Safety Monitoring Plan (DSMP) and the narrative in the PRMS section in the most recent CCSG application, and will serve as an instruction on how to implement the PRC procedures.

More information about the NCI –designated Cancer Centers and its directions can be found on page 27 of the CCSG Guidelines (Parts I, II &III), Section 9.2 PRMS at http://cancercenters.cancer.gov/downloads.html .

More information about Institutional Data and Safety Monitoring Plan can be found on this web site: http://www.medicine.virginia.edu/research/research-centers/cancer-center/cancer-research/dsmc

The relevant excerpt from the PRC narrative that was approved as part of the last competing renewal can be found in section 9.2 from CCSG application.

II. PRC Review Criteria

Determining whether a protocol should be reviewed by PRC

The focus of the PRC review is on protocols that recruit cancer patients, or ask a cancer-related question. PRC Coordinator makes the decision if PRC review is required based on the following:

a) Does the protocol have focus on recruiting patients with cancer or asks a cancer-related question?
b) Is goal of the protocol to detect or diagnose cancer?
c) Does the protocol have intent to treat cancer?
d) Does the protocol have intent to treat the sequelae of cancer?
e) Does the protocol have intent to prevent cancer's occurrence or recurrence?
f) Does the protocol have intent to develop a tool to diagnose, detect, or treat cancer (such as a new scanner or new surgical technique)?
g) Does the protocol have impact on the care of cancer patients that do not have a specific cancer focus?
h) Does the protocol have intent to prospectively gather information from cancer patients?
i) Does the protocol have intent to study any of the above, or to study samples taken or information gathered from cancer patients?

"Cancer focus" needs to be defined, but often it can only be identified in the context of the research being done:

Example 1

A protocol that was written to recruit cancer survivors along with heart attack survivors and patients who have undergone open heart surgery or transplant to study their health care experience during and after the medical intervention. This protocol has no specific interest in the cancer itself, and would be exempt from PRC review.

Example 2

A protocol that was written to recruit only cancer patients who had undergone chemotherapy or radiation in order to study their sleeping habits and quality of life since the therapy. This protocol means to gather more information on the sequelae of cancer and the impact on survivors and would need to be reviewed by the PRC.

Example 3

A protocol that means to test a new surgical adhesive that dissolves as the surgical wound heals that will be tested in patients undergoing lung surgery, which includes but is not limited to patients with lung cancer. This protocol looks to be exempt at first glance, however, for a certain section of the lung cancer population, surgery is standard of care, and because a change in treatment from the standard of care should be reviewed carefully, and because a successful trial may mean a change in the standard of care, it should be reviewed. This protocol was actually reviewed by the PRC.

Example 4

A protocol to test a new medication for long-term depression that recruits patients with long-term illnesses. Depression is a well-known sequelae of cancer, but this protocol has no specific cancer focus and would be exempt from review.

If the coordinator is unsure as to whether any given protocol should be reviewed, the protocol should be referred to the Chair for a decision.

What protocols require PRC review?

1. **All therapeutic and non-therapeutic interventional trials** (i.e. prevention, supportive care, screening, early detection, diagnostic studies) require review from the full Committee. Full board reviews require two medical reviewers, a biostatistician review, a CRC review, a DSMP review, and a review from the investigational pharmacist if drugs involved. The PRC seeks review from *ad hoc* reviewers when needed if the Committee members are not qualified to adequately review the proposed study.

2. **Non-interventional protocols** (i.e. epidemiologic, observational, correlative studies) are reviewed solely by the Chair of the PRC or his designee, using the same criteria as used for reviews from the full Committee.

3. **NCI Cooperative groups** are administratively reviewed by PRC Coordinator. More information about NCI cooperative groups can be found on:http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group.

   NOTE: Although protocols sponsored by the NCI national cooperative groups have already gone through the peer review group process, they must receive an administrative review by the PRC Coordinator to ensure that accrual information for these trials is entered to OnCore database.

4. **Non-therapeutic interventional trials** may undergo expedited review if deemed appropriate by the Chair. This includes trials like blood draws, tissue samples from biopsies, imaging, et cetera.

As a rule of thumb, the dividing line that determines full board review from administrative review is the level of intervention involved in the protocol. The greater the intervention, the greater risk to the patient, and the more stringent the review should be.

Expedited reviews are typically done by the Chair. In addition if there is a statistical plan, a statistician review should be obtained.

What Protocols DO NOT require PRC review?

PRC review is not required if the protocol is:

- Database protocols (protocols to establish or renew a database). This is not research.
- Retrospective chart review (this is not research either, as there is no hypothesis being “tested”, only data being gathered that may result someday in the prospective testing of a hypothesis).
- True epidemiology protocols (these are retrospective studies)
- Protocols involving cancer patients that do not have a cancer focus (see above).

NOTE: The PRC Coordinator determines if the trial is appropriate for PRC review. If it is not clear if a trial is appropriate for PRC review, then the chair is consulted.

Although these protocols do not require PRC review, they must be entered into OnCore if they have a cancer focus since cancer center is required to monitor and report to NCI number of protocols reviewed by PRC and monitor accrual to cancer-related protocols.

There is a subfolder -on the o: / drive named "PRC-Exempt" and these protocols, and all communication related to them, goes in that folder for easy reference.

In addition, IRB may request review of certain protocols that normally would not be reviewed by the PRC. This type of review occurs infrequently.

NOTE: If a trial appears to be a high or medium risk trial according to these definitions, it should not be expedited.

The low risk trials and trials that do not require PRC review present more of a "grey area" in terms of review. The variety of research methods and research interests at UVa makes it difficult to predict all possibilities. The **rule of thumb is that the more intense the intervention, the more intense the review should be also**. If the coordinator is unsure, the Chair should be consulted.

III. Submission process to PRC

****All PRC Submissions should be completed via the OnCore system****

Prior to submission of the protocols to OnCore all protocols need to have IRB Application created in IRB Protocol builder. Protocols are then submitted to PRC through OnCore. Protocols will be managed depending on level of review. PRC Chair, with the assistance of the PRC coordinator, determines if protocol requires full committee review, if it's eligible for administrative review, or if it requires no review by the PRC.

ePRMS Guidance document illustrates step-by-step directions for ePRMS management of the protocols in OnCore. This document is located at: https://oncore.med.virginia.edu/sop/ and explains in details how to:

- Assign PRC reviewers
- Entering reviews and findings
- Responding to PRC decisions
- Reports
    - There are four reports that are sent to the PRC along with the review assignments. These should be run at the time that protocols are assigned, and should be saved electronically using the snapshot format in a folder for documenting the meeting. This folder should also be used to save the minutes.
    - Monthly accrual report
    - Agenda Report/Expedited review
    - Competition monthly report

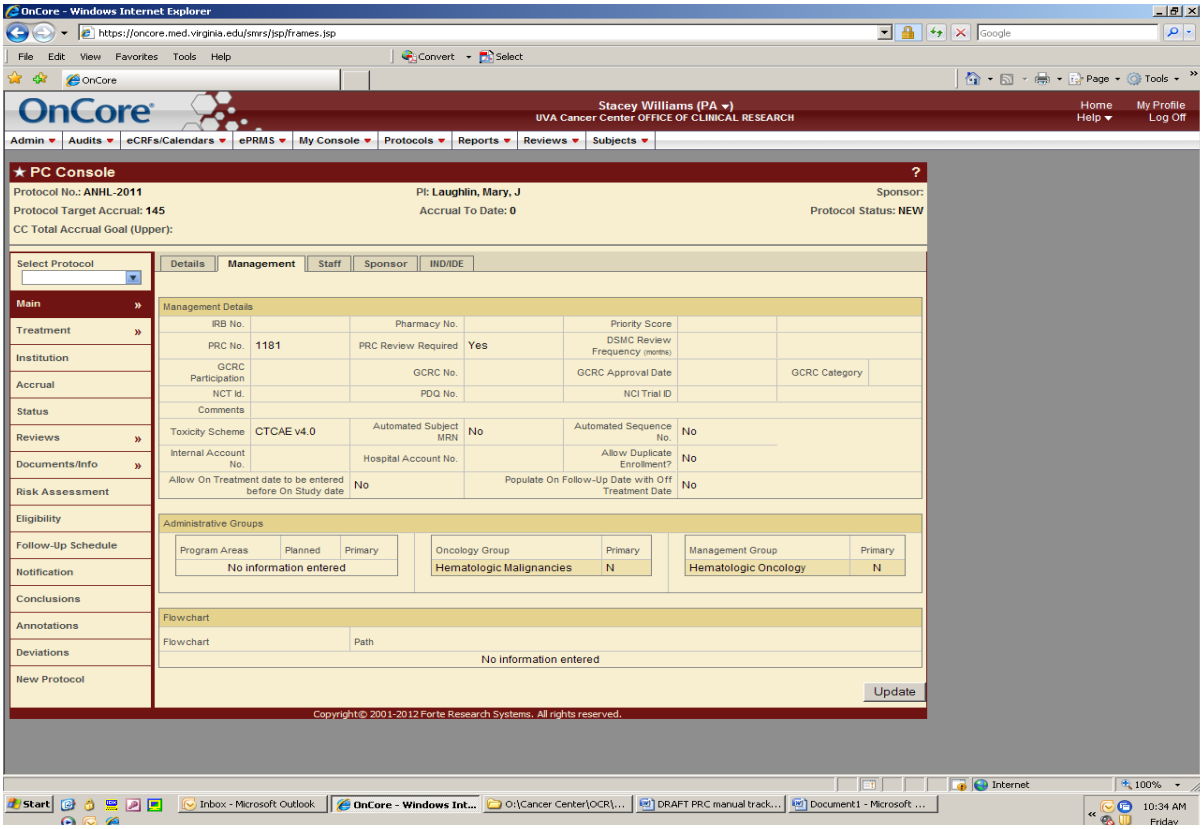
Assigning PRC Numbers:

The PRC Number should be entered by the PRC Coordinator as soon as the initial submission appears in the ePRMS console.

The PRC number is assigned by the PRC Coordinator on the management tab of the OnCore PRC Console. To determine the PRC number, the PRC Coordinator uses the Initial OnCore submission number assigned to the protocol, which located on the ePRMS tab, and then adds 1000 to it. For example:

OnCore submission number is 136. Then the PRC Number would be:

136+1000=PRC # 1136



NOTE: If all numbers in the 1000 sequence have been used, then the PRC Coordinator should use the next sequence, (2000, 3000, etc.)

Documentation required for initial PRC review:

- IRB protocol or IRB Application
- Sponsor Protocol (if applicable)
- Investigator's Brochure (if applicable)
- CRFs (if applicable)
- Any document deemed necessary by the PRC to complete a thorough review

Full Committee Protocols Submissions

****Full Committee protocols need to follow submission deadlines located at:**

http://www.medicine.virginia.edu/research/research-centers/cancer-center/cancer-research/prc

- Investigators create an application through IRB Protocol builder. Detailed instructions on how to submit the protocol for IRB are available at http://www.virginia.edu/vpr/irb/hsr/submit_protocol.html.

- Investigators submit protocols to PRC through ePRMS dashboard in Clinical Trials Monitoring System (OnCore). PIs upload protocol relevant documents to OnCore. All applicable documentation (a protocol, IRB application and, if applicable, investigator's brochure[s], surveys, quality of life questionnaires, and other tools) is submitted to OnCore by noon on the 2nd Monday of each month.

- PRC Coordinator conducts administrative review of all submitted documentation for completion. After reviewing all protocols to determine whether submissions are complete, the PRC Coordinator makes recommendations to the Committee Chair as to the required level of review using the criteria described above

- PRC Coordinator places each application on the next available agenda.

- Once placed on an agenda, the PRC Chair or Vice Chair, with assistance of PRC Coordinator, assigns two primary MD reviewers to each protocol. If an assigned PRC reviewer is unable to perform review of the protocol, he/she will notify the PRC Coordinator so that another reviewer can be assigned.

- Prior to the meeting, committee members review the entire submission and complete a full committee review form (see appendices for review template forms).

- Each reviewer is required to comment on the following:

    - Scientific merit of the study
    - The adequacy of the data and safety monitoring plan
    - Potential conflict of interest
    - Priority of the trial in relation to patient resources and staff support
    - Relevance of the proposed trial to the mission of the UVa Cancer Center

- Each reviewer e-mails their review to the PRC Coordinator by noon on the 4th Monday of each month when virtual meeting or meeting in person occurs.

- In addition to MD review, each protocol is reviewed by a biostatistician, a research coordinator, an investigational pharmacist if applicable, and IRB-PRC Coordinator.

- Investigators submitting therapeutic clinical trials must provide objective evidence supporting their ability to accrue to the study based on prior experience with a similar patient population. Investigators provide statements on competition with other active protocols, and the Committee reviews the statements for the purpose of non-approval of protocols that directly compete with an open or pending institutional or NCI-sponsored trial.

- If direct competition exists between or among studies, the Committee assigns priority as follows:
    1. UVA investigator-initiated trials receive first priority;

2. non-UVA investigator-initiated trials receive second priority;
3. cooperative group protocols, third priority;
4. industry-sponsored protocols, fourth priority.

PRC meeting minutes should contain the statement about competition assessment if competition in fact exists. The minutes should reflect what the plan is for dealing with it and whether or not the plan is acceptable.

If competition seems to be unacceptable, the PIs of the competing protocols should be contacted and asked for comment. The status of both protocols and the intentions of both investigators should be sounded. If there is no other remedy, the protocol with the higher priority should be allowed to go forward, and the other should be closed (if open) or withdrawn from consideration (if not yet approved by PRC).

- After the meeting and all reviews are received PRC Coordinator sends PRC Response letters to the study team via OnCore within 5 days of the meeting via OnCore. These letters are copied to the appropriate PRC members.

- If responses or clarifications are requested, the study team must do so within 120 days or the protocol will require full board re-submission.

- After receipt of an administrative Contingent Approval response, the PRC Coordinator reviews it for completeness and relays the response to the PRC Chair or Vice Chair.

- The PRC Chair or Vice Chair reviews the response and documents that all concerns are adequately addressed and that the protocol is revised appropriately.

- The protocol is given approval. (PRC will not approve the protocol until all concerns are addressed).

- An approval is sent to the study team within 5 days

Once a protocol has undergone full board review, subsequent submissions may be expedited except in the case of a major design change, such as adding a dose level or an investigational agent. The PRC Coordinator issues an approval form which notifies the PI, study team and the IRB/PRC Coordinator when approval is granted. Protocols must be approved prior to IRB submission.

Expedited Protocol submissions

**Trials appropriate for administrative review are submitted and reviewed independently of the monthly deadline for full committee review.

- Investigators create a protocol or application through IRB Protocol builder. Detailed instructions on how to submit the protocol for IRB are available at http://www.virginia.edu/vpr/irb/hsr/submit_protocol.html.
- Investigators submit protocols to PRC through ePRMS dashboard in Clinical Trials Monitoring System (OnCore). PIs upload protocol relevant documents to OnCore. All applicable documentation (a protocol IRB protocol/IRB application and, if applicable, investigator's brochure[s], surveys, quality of life questionnaires, and other tools) is submitted to OnCore on a rolling basis.

- PRC Coordinator conducts administrative review of all submitted documentation for completion. After reviewing the protocol to determine completeness, the PRC Coordinator sends protocol recommended for expedited review to the Committee Chair or Vice Chair. If the trial is re-submitted in response to full board review, any reviewers who had comments or questions will be copied for review

- The PRC Coordinator then assigns the study to the PRC Chair or Vice Chair for review. When the review is completed by the Chair or Vice Chair, a review outcome memo is issued to the study team within 5 (response to full board submission) or 14 days (initial expedited submission.)

- The Chairman or Vice-chairman of the PRC reviews and comments on the following:
    - Scientific merit of the study
    - The adequacy of the data and safety monitoring plan

    - If any changes are needed PRC Coordinator will communicate with PI via e-mail.

    - After receipt of response to PRC Review from PI, the PRC Coordinator reviews it for completeness and relays the response to the PRC Chair or Vice Chair.

    - The PRC Chair or Vice Chair will review all responses prior to giving final approval.

    - PRC Coordinator and PRC Chair will review revisions to make sure that all concerns are adequately addressed and that the protocol is revised appropriately within 5 or 14 days of receipt of response

    - An approval is sent to the study team within5 or 14 days.

    - PRC Coordinator will send final approval to IRB.

NOTE: If the PI submits a response to the initial PRC review within four months (120 days), the issues can be addressed and protocol can consequently be approved. If the response returns after four months have elapsed, the protocol must undergo another full Committee review.

IV. PRC Meetings

Organizing the PRC meeting

The Protocol Review Committee meets a minimum of once per month. If there is sufficient demand, additional meetings are called. The PRC meetings are held on the fourth Monday of each month. In case of holiday, the PRC meeting will be held the day after the holiday. All timelines will be shifted appropriately to incorporate the holiday schedule. Minutes of the meetings are documented.

A copy of the schedule of meetings is available at this address:
http://www.medicine.virginia.edu/research/research-centers/cancer-center/cancer-research/prc

The following are the steps for organizing the meeting:

1. The meeting will be documented and orchestrated through OnCore.
2. All required Protocol Review Committee documentation is received through OnCore by the PRC Coordinator by noon on 2nd Monday of each month.
3. The Protocol Review Committee Coordinator organizes all received submissions.
4. PRC Coordinator, with assistance from PRC Chair, will then assign primary MD reviewer for each protocol. PRC Coordinator will send an e-mail to all reviewers with attached documentation for all of the protocols on the agenda for that meeting s by the end of business day on the 2nd Wednesday of each month. This gives each reviewer ample time to complete their review. If an assigned PRC reviewer is unable to perform review of the protocol, he/she will notify the PRC Coordinator immediately so that another reviewer can be assigned and given ample time for review
5. Each committee member assigned to review a study will e-mail their review, using the appropriate PRC templates for each reviewed protocol to PRC Coordinator by noon on the 4th Monday of each month.
6. On the 3rd Wednesday of each month, the PRC Coordinator sends out a reminder to each assigned reviewer via e-mail that reviews are due by the 4th Monday of each month (date).
7. On Friday prior to the PRC meeting and again on the following Monday, PRC Coordinator will send another reminder via e-mail to all reviewers that reviews are due at noon Monday.
8. Each committee member assigned to review a study will e-mail their review, using the appropriate PRC templates for each reviewed protocol to PRC Coordinator by noon on the 4th Monday of each month.
9. Once all reviews are received, the PRC Coordinator will disseminate via e-mail reviews to all PRC members by close of business day on the 4th Monday. Each member is required to read all reviews for each protocol and to vote, within 48 hours, using the following guidelines:
10. At least two MDs besides the chair must cast a vote. When voting, the majority decision rules and in case of a tie, the PRC chair casts the deciding vote. PRC Response letters will be issued with comments as appropriate to the study team within 4 days of the electronic meeting. If responses or clarifications are requested, the study team must do so within 120 days or the protocol will require re-submission and re-review.
11. When revisions/clarifications are received for "Contingent or Deferred" trials, the PRC coordinator will confirm that all previous PRC requests have been addressed and appropriate study documentation has been received prior to sending it to the committee for final review. The Chair and all appropriate committee members will review all revisions/clarifications within 3 days of receipt and issue PRC approval letter if appropriate.
12. If protocol receives majority vote of "Clarification Contingent or revision of Deferred Protocol, revisions required and we wish to see the revised protocol" then, within 24 hours, the PRC Coordinator will confirm all previous PRC requests have been addressed and forward all documentation and responses back to all assigned reviewers. Reviewers have 8 working days to respond with comments. If there are no additional comments or requests, PRC Coordinator will issue approval letter and send to study team within 2 weeks.
13. If protocol received a majority vote of "deferred" or "not approved as written," the PRC Coordinator will issue a letter within 4 days from the electronic meeting. All protocols that

are rejected during their initial submission to the PRC must go through full board review during subsequent submission.

14. In lieu of Minutes in electronic meetings, the reviewer's comments will serve as the Meeting minutes.
15. All emailed comments are used to create meeting minutes
16. In case of holiday, the PRC meeting will be held the day after the holiday. All timelines will be shifted appropriately to incorporate the holiday schedule.

The PRC Coordinator sends the PRC minutes to the committee for comment. The final approved minutes become the official record of the meeting. Minutes are also shared with the IRB monthly via e-mail.

Collecting and filing reviews

Reviews are generally due within two weeks of assignment. It is helpful to send reminders every Monday until all reviews are received. Reminders that cc a medical reviewer's admin assistant are more likely to produce a review.

There is no paper file for each protocol reviewed, so it is imperative that complete electronic files are kept and are clearly labeled. Otherwise answering questions about reviews, preparing reports, or preparing for the site visit will be difficult.

Reviews are saved in an electronic file on the F drive according to the kind and number of the submission and the reviewer's name. If a review is sent on paper only it should be scanned and saved to the F drive. See the section on naming conventions to save reviews.

Initial review PRC response letter for Full Board protocols

The PRC response letters are addressed to PI and contain the following elements:

- The protocol by PRC number and protocol ID
- The date of review and whether the review was expedited or agenda
- The finding of the PRC for both the protocol and the DSMP
- Any comments for revision or response

It is addressed to the PI and cc'd to the person who submitted the protocol (most of the time regulatory coordinator or to more people if requested).

PRC review letter contains comments from the reviewer's written review forms and/or from the comments made during the meeting. The written comments should be proofread carefully and rephrased where needed; Chair must review all PRC letters before they are sent to PIs...

Review of responses to PRC initial review

Once a protocol has undergone full Committee review, subsequent revision to the protocol may be expedited except in the case of a major design change, such as adding a dose level or an investigational agent. All protocols must be approved by the PRC prior to IRB submission.

V. PRC review of modifications

PRC needs to review certain modifications of previously approved protocols.

Full Board Modifications

Modifications that involve one or more of the following revisions should go back to the **full PRC committee** for review:

- protocols that are considered "deferred" or "not approvable as written"
- significant changes in therapeutic design (e.g. adding or subtracting a dose level)
- significant changes in protocol eligibility criteria such as adding a new indication or identifiable patient population.

All revisions (modifications) of the UVa investigator initiated protocols that have been classified as high- or medium risk and that are overseen by the Cancer Center's Data and Safety Monitoring Committee (DSMC) will be reviewed by full committee. The same review process and the same timelines for review and responses are used as in a review of new protocols that require full committee review. If a revision of an institutional protocol changes the protocol's design, the risk level may be reassessed.

Expedited Modifications

All minor revisions (modifications) of the previously PRC approved protocols will be submitted for administrative review. The same review process and the same timelines for review and responses are used as in a review of new protocols that require administrative review. When the review is completed by the Chair or Vice Chair, a review outcome memo is issued to the study team within 5 days of submission.

Documents required to be submitted for Modifications:

- Revised protocol with tracked changes
- IRB protocol/IRB Application (if applicable) with tracked changes
- Documentation (letter, email, etc.) detailing all changes made to the protocol
- Any other protocol documents if affected by modifications

Exempt revisions or modifications:

- Revisions that are solely administrative (e.g. typos, minor formatting changes)
- Revisions that are made solely to update the list of investigators
- Revisions to pharmaceutical-sponsored protocols
- Revisions to protocols that were exempt from PRC review originally
- Revisions to protocols that do not have a cancer focus but the IRB requests confirmation that the PRC does not need to review the revision

VI. Withdrawals of previously reviewed protocols

Principal Investigators (PIs) of new protocols not approved by the full committee are given 120 days to respond (from the time of notification of review outcome). If no response is received after in 60 days, reminder correspondence is sent to the PIs informing them that the protocol will be withdrawn if response is not received within the following two months. Any unapproved protocols without a response within six months from the time of original notification of review outcome will be

automatically withdrawn by the PRC. If PIs wish to reactivate the protocols following withdrawal, they must begin the protocol application process from the start as a new submission. PIs can withdraw protocols themselves at any time with sending a reason for withdrawal.

VII. Risk Classification

The risk level (high, medium, low or exempt) and the DSMP template (full or abbreviated) that is required are based on the level of the intervention, which determines the impact on or risk to the patient. It is unlikely that a protocol with intense intervention would ever have an abbreviated DSMP, but determining what level of DSMP is appropriate for a low-intervention protocol is sometimes difficult.

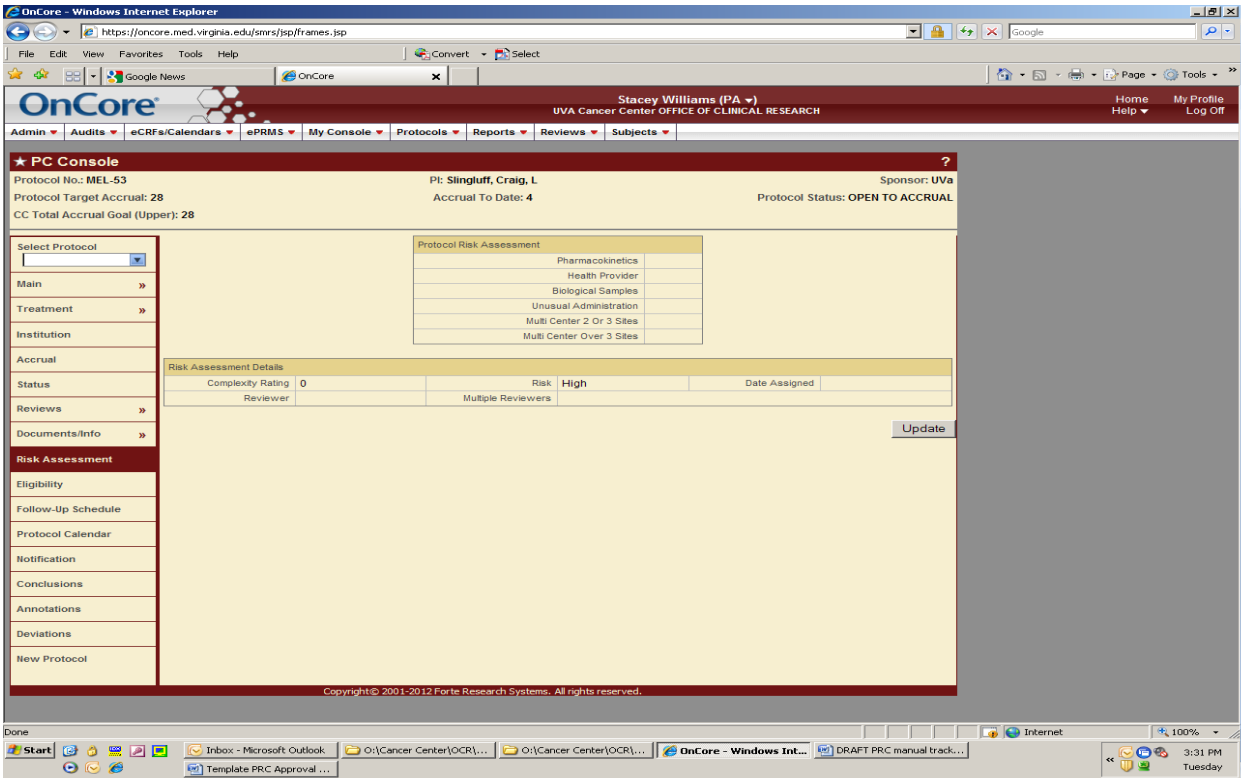
When a protocol is submitted, first determine whether it should be expedited or go to agenda review.
If it is to go to agenda review, the medical reviewers will assign risk level using the PRC review template (appendix C) and the DSMP will be assessed by the PAM monitors. The medical reviewers will review the list of expected AEs for the protocol intervention and determine whether it is appropriate. Agenda-review protocols are usually medium- or high-risk. The coordinator does not need to do any assessment of these DSMPs.
The PRC will assign a risk classification level that will dictate the level of monitoring by the DSMC for each study using the following guidelines:

- High risk: investigator-initiated INDs (regardless of phase), Phase 1 trials, gene therapy trials, and any other types of trials designated by the National Institutes of Health (NIH) as high risk
- Medium risk: all other interventional therapeutic trials (such as those using drugs, biologics or devices) not designated by NIH or PRC as high risk (typically phase II and phase III trials)
- Low risk: interventional non-therapeutic trials (no therapeutic intention, such as nutritional or behavioral trials, biopsy or blood sample collection)
- PRC review not required: non-interventional trials (epidemiology research, survey, imaging or functional assessment) monitoring plans are not needed). Interventional trials may not be classified as “PRC review not required.”

For expedited reviews, the DSMP is usually quite brief (two questions) and can be assessed by the PRC coordinator. Most protocols will use the abbreviated template provided by the IRB’s protocol builder program. To determine whether this is appropriate or not, check the list of the procedures that is covered by the abbreviated protocol template in the institutional plan. When using the abbreviated template:

- For protocols that are *low risk*, a statement should be added that the DSMC will provide oversight.
- For *exempt risk* protocols, the PI’s oversight is sufficient.

Enter the appropriate risk level in OnCore on the Risk Assessment tab located on the PC Console.



Exempt Risk Classification

1. If the protocol can't be linked to patient identifiers because it uses only already-banked tissue from TPF or another bank
2. Epidemiology research
3. Survey/ questionnaire (ex. protocol to collect data on sleeping patterns of teens with cancer diagnosis to compare to normal teens' sleeping patterns)
4. Imaging (comparing CT to MRI, etc)
5. Functional assessment or QOL-only studies

Protocols that meet these criteria but also have an intervention (like counseling or drawing blood or what have you) need a DSMP only for that intervention. The IRB has the two-question template for most of these built into Protocol Builder.

VIII. Review Outcomes

The following are possible outcomes of PRC review:

1. **Approved** (If the protocol is approved, no further action is necessary until the protocol is amended). PRC Approval form is granted.

2. **Contingent Approval** (not ready for forward movement; the concerns are such that the response need only be reviewed by the original reviewers).

    - Clarification or revision of the protocol is required.

- PRC Response Letter will contain a discussion of what concerns need to be addressed before approval is granted.

- This letter enumerates each concern and requires the PI or designee to respond to each concern point by point.

- PI should submit responses to questions noted in PRC Response Letter.

- Responses to a Contingent Approval go back to the original reviewers.

- The PRC Coordinator reviews the response for completeness and relays the response to all original reviewers. If an original reviewer is unavailable, a replacement reviewer is assigned by the Chair or Vice Chair. Reviewers are responsible for ensuring that all concerns are adequately addressed, and that the protocol is revised appropriately.

- If all concerns are addressed PRC approval is granted. PRC will not approve the protocol until all concerns are addressed.

3. **Deferred**: revision of the protocol is required. PI should submit responses to questions noted in PRC Response Letter (not ready for forward movement; the concerns are such that the response needs to be discussed by the full committee).
   - Revision of the protocol is required.

   - PRC Response Letter will contain a discussion of what revisions need to be made

   - This letter enumerates each concern and requires the PI or designee to respond to each concern point by point.

   - PI should submit responses to questions noted in PRC Response Letter.

   - Responses to a deferred outcome of the PRC review will go back to the full committee.

   - When responses to a deferred decision are received the PRC Coordinator reviews submitted documentation for completeness and puts the protocol on the agenda for the next meeting and assigns the protocols to all original reviewers. If an original reviewer is unavailable, a replacement reviewer is assigned by the Chair or Vice Chair. Reviewers are responsible for ensuring that all concerns are adequately addressed, and that the protocol is revised appropriately.

   - If all concerns are addressed PRC approval is granted. PRC will not approve the protocol until all concerns are addressed.

4. **Reject Not Approved**-(the protocol maybe submitted again as a new submission if the study team desires to rewrite)
   - Revision of the protocol is required.

- PRC Response Letter will contain a discussion of what concerns need to be addressed
- This letters enumerate each concern and require the PI or designee to respond to each concern point by point.
- PI should submit responses to questions noted in PRC Response Letter
- Responses to a Rejected outcome of the PRC review will go back to the full committee.
- When responses to a Rejected protocols are received the PRC Coordinator reviews it for completeness and e and places protocol on the next available agenda.
- The protocol is reviewed by the full committee and is evaluated in the same manner as new protocols, with the same possible outcomes: Approved, Contingent Approved, Deferred or Rejected.
- If an original reviewer is unavailable, a replacement reviewer is assigned by the Chair or Vice Chair.
- Reviewers are responsible for ensuring that all concerns are adequately addressed and that the protocol is revised appropriately. These reviews are included in the deliberation of the committee.
- If all concerns are addressed PRC approval is granted PRC will not approve the protocol until all concerns are addressed.

Granting PRC Approval

The Chair must approve in writing all protocols and revisions. This is done via e-mail to PRC Coordinator. For documentation purposes the Chair's approval should be saved in PRC files on the o-drive (**pathway: O:\Cancer Center\OCR\OCR DSMC & PRC Monitoring\PRC\Protocol Review Committee**) and in OnCore.

Creating Approval Letter (Appendix D):

Please use OnCore to fill out the appropriate information on the PRC Approval Letter:

- Enter Date, PRC # and Study Title in appropriate areas
- Enter IRB Submission # (located on IRB Application or IRB Protocol) or IRB # (OnCore PC Console Management Tab)
- Enter PRC approved IRB approved application/protocol version date (if applicable) or PRC approved Sponsor's protocol version date (if applicable)
- Enter Study Phase and study type (located on ePRMS Coordinator's Console & PC Console)
- Enter risk level assigned by Physician reviewers. Please note the following:

  - Low risk: risk ratio assessment should always be deemed as not involving greater than minimal risk
  - Medium: risk ratio assessment should always be deemed as greater than minimal but prospect of direct benefit or greater than minimal and no prospect of direct benefit
  - High risk: risk ratio assessment should always be deemed as greater than minimal but prospect of direct benefit or greater than minimal and no prospect of direct benefit
- PI and study team is required to report all patient accruals into OnCore on a monthly unless exempt. Exemption from accrual includes:
  - Database protocols
  - Protocols done under waiver of consent
  - Protocols with no patient identifiers
  - Protocols that utilize banked and unidentifiable specimen
- PI and study team is required to report all AE's to IRB, OnCore and sponsor as described in DSMP unless exempt. Exemption from reporting AE's includes:
  - Database protocols
  - Protocols done under waiver of consent
  - Protocols with no patient identifiers
  - Protocols that utilize banked and unidentifiable specimen
- Protocol Revisions:
  - PI is required to submit revisions to the PRC if:
    - Investigator Initiated trial
    - IRB requests that study be re-reviewed by PRC due to major scientific changes
  - PI is not required to submit revisions to the PRC if:
    - Pharmaceutical study
    - Non-UVA Investigator Initiated
- Responsible Oversight Body:
  - Investigator Initiated trial: UVA DSMC (phase 1-IIIA trials)
    - Medium and Low Risk trial- annual PAM audit
    - High Risk Trial- semi-annual PAM audits
  - Investigator Initiated trial: IIIB and up (DSMB-however, the DSMC and PRC must approval the DSMB charter and members)
  - Pharmaceutical Trials or Non-UVA Investigator Initiated: sponsor identified Medical Monitor or DSMB

Note: Physician reviewers must agree on the risk level and risk ratio assessment

IX. Performance monitoring of approved protocols

The PRC monitors accrual to all cancer-related clinical trials that enroll human subjects or that use clinical specimens that can be linked to individual patient or participant data. The purpose of the performance review is to highlight procedural issues that hinder accrual so that they can be addressed, and to close protocols that may be a drain on investigator resources.

Accrual monitoring begins at the time the study opens to accrual and ends when accrual is closed. The PI or study team enters accrual data into the Center Clinical Trials Monitoring System (OnCore) on a monthly basis. Protocols that use specimens that cannot be linked to patient identifiers are exempt from accrual reporting.

Preparation for semi- annual Performance Review

Reports are run by the Informatics team before the first of the month (May and November) in which the protocols are to be reviewed. The PRC Coordinator should QC the report received by Informatics to ensure that all protocols on the list meet the appropriate performance review monitoring criteria. Any compassionate use or "rare disease" trial should not receive a PRC Performance review.

Before drafting a letter re any protocol, check to see whether a) the protocol has been reviewed previously and if so, b) what the final letter from the PRC stated. Draft the performance review letters and send them to the Chair for review. They should be sent as close to the beginning of the month as possible, to allow the investigators time to respond and should be sent by the first of the month to the PI and copied to the CRC of record.

Letters state which protocols are up for review, the criteria for review, and which of the review criteria the listed protocol(s) met. The investigator is asked to respond by the next PRC meeting with a revised 12-month target estimate (first review), or either a plan to address the issues affecting accrual or to close the protocol (second review or more). If a protocol has been reviewed twice in a row, there should be a defensible reason for allowing it to continue. If a protocol has been reviewed twice but not consecutively, there is less impetus to close it unless the issues preventing accrual warrant it. All responses from the study team must be received prior to the meeting date (4th Monday of the Month)

Monitoring Accruals (Appendices D & E)

During the meetings in May and November the PRC reviews:

- studies that have been open for at least six months that have not accrued any registered patients and
- studies that have been accruing at less than 45% of the estimated accrual rate over the trailing six month period.

Performance review is based on the estimate of 12-month accrual given by the investigator at the time of PRC submission. If it is the first review for a protocol, the PRC will often ask the investigator to amend the 12-month target to something more reasonable.

The study can be closed by PRC if:

- No response is received from the study PI
- If study was reviewed for non-accrual or slow accrual at the previous review.
- for non-compliance (usually because of lack of reporting patient registration data) or for excessive risk to patients.

X. Closing protocols

The PRC can approve protocols, to prevent their opening to accrual (or activation), and to close protocols where appropriate. Please note that this closure means closure to accrual, and not complete closure, which would mean that all protocol activity, including treatment and follow-up, would have to end immediately.

PRC can close protocol due to:

- **slow accrual or non-accrual**
  Closure for slow accrual or non-accrual is usually a result of the semi-annual performance review, held twice yearly in May and in November. However, accrual and competition are priorities for any NCI-designated Cancer Center and so this is not limited to the scheduled performance review.

- **non-compliance**
  Closure for non-compliance is rare, but does happen. This is usually the result of the study team's failure to report monthly registration data or to respond to queries from the PRC Coordinator, though it is possible that the DSMC would request closure for non-compliance as well.

- **excessive risk to patients**
  Closure for excessive risk to patients has not been required as of the writing of this document, but is within the PRC's purview. In theory this might be prompted by an audit that reveals serious treatment issues or excessive toxicity.

- **at the request of the DSMC or the appropriate DSMB**
  Closure at the request of the oversight body is usually the result of an unacceptable audit. The oversight body must furnish the study team or PI with the reasons for requesting the closure and the conditions (if applicable) under which the protocol would be allowed to re-open. The oversight body would also notify the PRC of the request(s) to close and to re-open the protocol. It is the responsibility of the oversight body to ensure that all relevant conditions have been met.

NOTE: If the PRC recommends that a protocol be closed temporarily or permanently, a letter with this recommendation is sent to the PI, IRB and study sponsor.

PRC Closure Letter

A letter should be sent from the PRC to the PI explaining the reason for the closure to accrual and specifying a date by which the PI should have closed the protocol to accrual at the IRB. It should also specify what conditions must be satisfied in order to re-open the protocol to accrual, if applicable, and should also specify whether treatment and follow-up may continue while the protocol is closed to accrual.

If the protocol is a multisite protocol, the letter should also stipulate which sites are affected and which may continue accruing, if appropriate. The letter should also specify whether appeal is permissible and if so, the form that the appeal should take, to whom it should be addressed and a date by which it should take place. The date of the appeal should fall before the date of the deadline to close the protocol.

If the protocol is not closed to accrual by the date specified, a second letter should be sent to the PI and the chair of his or her department reiterating the reasons for closure and requesting that the PI contact the PRC Chair with his or her plan to close the protocol. This letter should also give a deadline for this plan and a clear statement of the PRC's being required by the NCI to close protocols in accordance with its stated policy, and a statement that the matter will be referred to the appropriate Dean after the deadline has passed.

XI. PRC review of DSMC recommendations

The PRC serves as the functional arm of the DSMC. Issues of concern (*e.g.,* adverse events, safety issues) are discussed at the DSMC meeting and then are reported to the PRC at the monthly meeting, which is held one week after the DSMC meeting. On DSMC recommendation, the PRC temporarily closes protocols to accrual until issues of concern are addressed. The DSMC may request that a protocol be closed permanently. In addition to safety concerns, study-closure criteria include lack of compliance with institutional requirements, including patient registration, AE/SAE reporting, data reporting; or general lack of compliance with the protocol-specific data and safety monitoring plan.

PRC acts as the action arm of the DSMC and will close protocols to accrual at the request of the DSMC.

XIII. Filing Documentation

All PRC documentation is contained within the ePRMS console in OnCore and the Protocol Review Committee Folder on the O: / drive (pathway: O:\Cancer Center\OCR\OCR DSMC & PRC Monitoring\PRC\Protocol Review Committee) and in OnCore.

XIV. Naming conventions for PRC Files

Reviews, protocols, and revisions (the electronic protocol review file) are saved in an electronic folder rather than a paper file. Each protocol uses a number system to keep the different submissions and reviews and approvals in sequential order. Reviews may be word documents or may be e-mails, and responses from the PRC may also be word documents or e-mails.

The number corresponds to how many times a submission have been received for the protocol. The first time a protocol is submitted, it has no number. The second submission may be a response letter or a revision (submission 2). The next submission will be submission 3, submission 4, et cetera.

XV. IRB

All cancer-related trials must be approved by IRB. Most of the protocols that are reviewed by the PRC are reviewed by the IRB-HSR. More information about IRB-HSR processes can be found on this site: http://www.virginia.edu/vpr/irb/hsr/index.html

The PRC works in cooperation with the IRB to ensure that the PRC reviews all cancer-related protocols at UVa. This cooperation has 3 components:

1. The PRC coordinator and Chair receive all IRB agendas and review them to verify that all submissions meant for full-board review have received PRC approval prior to IRB review.

2. The IRB requires PRC approval for all cancer-related protocols, whether full-board or expedited, prior to review.
3. The PRC coordinator has query access to the IRB database and can check the status of protocols and/or IRB review.

The PRC also shares meeting minutes with the IRB intake officer for full-board review in order to aid the IRB's scientific review.

XVI. Appendices

Appendix A: PRC review templates

UVA Cancer Center Protocol Review Committee Review Template

Date: _____

PRC #: _____ Investigator: _____ Reviewer: _____

Title:

Protocol Origin:
Institutional☐
Pharmaceutical Sponsor☐
Cooperative Group: (specify)☐
Non-UVA Institutional☐

Has there been prior scientific review (e.g. CTEP, NIH)? ☐ Yes ☐No

Study Objectives:

Relevance and completeness of background information:

Study Design:
Clarity and appropriateness of eligibility criteria:

Outcome measures:

Consistency of outcome with study objectives:

Feasibility of achieving study objectives:

Suitability of methods (incl. appropriate blinding/masking procedure, appropriate randomization):

Implications of this study: (i.e. increased survival, remissions, decreased toxicity)

Conflict with other protocol(s): ☐Yes ☐No
Protocol Number(s) _____ Protocol
Priority_____

Protocol Comments/Specific Problems (specify):

Significance/Relevance:	☐High	☐Medium	☐Low
Originality/Innovation:	☐High	☐Medium	☐Low
Overall Scientific Merit:	☐High	☐Medium	☐Low

Overall Scientific Assessment:
☐ Outstanding (outstanding science with virtually flawless implementation)
☐ Excellent (excellent science with issues that can be easily addressed)
☐ Very good (meritorious science with substantial revision required)
☐ Unacceptable

Risk Category:

☐ High risk: sponsor-investigator INDs (regardless of phase), Phase 1 studies, gene therapy trials, and any other types of trials designated by NIH as high risk
☐Medium risk: all other therapeutic intervention (such as drugs, biologics or devices) trials not designated by NIH, PRC or IRB as high risk (typically phase II and phase III trials)
☐ Low risk: non-therapeutic intervention trials (no therapeutic intention, such as nutritional or behavioral trials, biopsy or blood sample collection)
☐Exempt: non-intervention trials are exempt from providing a monitoring plan (such as Epidemiology research, survey, imaging or functional assessment). Intervention trials may not be classified as' exempt.'

Risk - Benefit Ratio:
☐ Not involving greater than minimal risk
☐ Greater than minimal risk, but prospect of direct benefit to patient
☐ Greater than minimal risk and no prospect of direct benefit

Risk Level Assigned corresponds with Risk level section of DSMP (Question #3 under Protocol Review Committee Requirements Section of IRB Application or Protocol):
☐ Yes
☐ No-see below:
____ High risk should be checked and Table A entered
____ Medium risk should be checked and Table B entered
____ Low risk should be checked and Table C entered

Overall Review Recommendations:
☐ Approve d.
☐Contingent Approval (Clarifications required)
☐ Deferred (Mandatory Revisions required)
☐ Not Approved

Biostatistician Review Template

Study Title:

PI: Reviewer: Date:

PROTOCOL: STATISTICAL CRITERIA	
(Check all that apply) Phase of Trial	Pilot/Feasibility ☐ Phase I ☐ Phase II☐ Phase III☐ Phase IV☐ Non-Therapeutic ☐
Randomization	Randomized☐ Non-Randomized☐
Blinding	Single- Blinded ☐ Double-Blinded☐ Open Label☐
Accrual	_____ Total Number of patients
Total Duration	_____ months
Y ☐ N☐	Interim Analysis planned? If so, after how many patients enrolled?
Y ☐ N☐	Sample Size estimation appropriate? Is the statistical power analysis sufficient to address the study hypothesis? **(If not, state issues in summary section below)**
Y ☐ N☐	Inclusion of Stopping Rules
Y ☐ N☐ N/A ☐	Statistical Analysis method appropriate? **(If not, state issues in summary section below)**
Primary Outcome	
Summary Section	
Overall Statistical Review Recommendations: ☐ Approved ☐Contingent Approval (Clarifications required) ☐ Deferred (Mandatory Revisions required) ☐ Not Approved	

PROTOCOL REVIEW COMMITTEE

CLINICAL RESEARCH COORDINATOR REVIEW TEMPLATE

Study Title:

PI: Reviewer: Date:

PROTOCOL: ELIGIBILITY CRITERIA	
Y ☐ N☐	All eligibility criteria listed matches the primary, secondary endpoints and intent of the trial
Y ☐ N☐	Appropriate labs (pregnancy, blood draws, urine, etc.) are listed in protocol and will be completed at the appropriate intervals
Y ☐ N☐	Patient registration/ randomization section is complete
Y ☐ N☐	**Subject** stopping rules are included in protocol
Y ☐ N☐ N/A☐	All questions in IRB Protocol have a response
Y ☐ N☐ N/A☐	IRB Application and Sponsor's Protocol correspond with each other.
Y ☐ N☐	N/A ☐ Plan for breaking the blind given and appropriate
Y ☐ N☐	Classification and grading system of AEs listed and appropriate
Y ☐ N☐	Attribution scale designated and appropriate
Y ☐ N☐	Plan to report expedited AEs and SAE/AE to IRB and CC DSMC as appropriate
Y ☐ N☐	N/A X Plan to report SAE/AE to FDA.
Y ☐ N☐	N/A ☐ Plan to report SAE/AE to Sponsor.
Y ☐ N☐	N/A ☐ For multi-site trials, plan to report SAE to other participating sites
DATA MONITORING	
Y ☐ N☐	Specific elements are listed for data/aggregate review.
Y ☐ N☐	A frequency of data and safety monitoring is given.
Y ☐ N☐	A person has been designated to be responsible for data review.

Y ☐ N☐	Identifies how data will be managed and made available for review
RESOURCE AVAILABILITY	
Y ☐ N☐	Are there existing facilities (or a commitment for such) available?
Y ☐ N☐	Is the time allotted to study personnel adequate for the proposed work?
Y ☐ N☐	Are the study aims likely to be accomplished in the time projected?
Overall Review Recommendations:	
☐ Approved ☐Contingent Approval (Clarifications required) ☐ Deferred (Mandatory Revisions required) ☐ Not Approved	

CANCER CENTER DATA AND SAFETY MONITORING PLAN REVIEW

PRC#:
Study Title:
Sponsor's Protocol Version:
IRB Application Version:
Sponsor:

PI: **Reviewer:** Parks, Ng **Date:**

SAFETY MONITORING PLAN	
Y ☐ N☐	All expected risks are listed. -
Y ☐ N☐	N/A ☐ If the study is a UVA investigator initiated and the CC DSMC has oversight, is the maximum grade given with expected risks?
Y ☐ N☐	Specific parameters are listed for safety review- -
Y ☐ N☐	A frequency of safety observation is given -
Y ☐ N☐	**Subject** stopping rules are included in the safety monitoring plan. Dose modifications are given when appropriate and are reasonable. -
Y ☐ N☐	Classification and grading system is listed, appropriate and consistent. -
Y ☐ N☐	Attribution scale designated and appropriate -
Y ☐ N☐	Instructions regarding reporting of expedited AEs and SAE/AE to IRB are given.
Y ☐ N☐	N/A ☐ Instructions for reporting SAE/AE to FDA are given. -
Y ☐ N☐	N/A ☐ Instructions for reporting SAE/AE to Sponsor are given. For trials with UVA CC DSMC oversight, the tables per the institutional plan are in the sponsor protocol. -
Y ☐ N☐	N/A ☐ For UVA studies with CC DSMC oversight, instructions are listed for reporting of accrual, adverse events and data into Oncore?
Y ☐ N☐	N/A ☐ UVA investigator initiated, multi-site trials with CC DSMC oversight, outlines how data is to be made available from other sites and in what time frame.
DATA MONITORING	
	Who is responsible for monitoring the progress and safety of the study? ☐ PI ☐ Safety/Medical Monitor ☐ sponsor ☐ UVA CC DSMC ☐ Outside DSMB ☐ Other: -
Y ☐ N☐	Is the monitoring agent appropriate for the study?
Y ☐ N☐	Specific elements are listed for data/aggregate review.

	-
☐ ☐ ☐ ☐	Approved. Contingent Approval (Clarifications required) Deferred (Mandatory Revisions required) Not Approved
	Notes:

Pharmacy Review Template

Study Title:

PI: Reviewer: Date:

PROTOCOL: PHARMACY CRITERIA	
Y ☐ N☐	Dosing Administration appropriate **(If no, please comment in Summary Section)**
Y ☐ N☐	Treatment Schedule appropriate? **(If no, please comment in Summary Section)**
Y ☐ N☐	All expected side effects documented? **(If no, please comment in Summary Section)**
Y ☐ N☐	Management of adverse effects appropriate? **(If no, please comment in Summary Section)**
Y ☐ N☐	Dose reductions appropriate? **(If no, please comment in Summary Section)**
Y ☐ N☐	All prohibited premedications and medications listed? **(If no, please comment in Summary Section)**
Summary Section	
Overall Statistical Review Recommendations: ☐ Approved ☐Contingent Approval (Clarifications required) ☐ Deferred (Mandatory Revisions required) ☐ Not Approved	

Appendix B: PRC Response Letter

The Cancer Center

University of Virginia HEALTH SYSTEM

James Larner, MD
Director and Chairman

Stacey Williams
PRMS Coordinator

<Date>

<PI>

<Title>
Department of <Department Name>
Box <Number>

Re: PRC< # > "Title"

Dear <PI Name>:

The protocol and data and safety monitoring plan were reviewed by the PRC committee members during the <Meeting Date> meeting. <The Committee does not feel that this protocol can be approved as written (Deferred or not approved), The Committee finds that the Protocol and DSMP needs further clarification (Contingent), or The committee approves the protocol as written (approved).> <Mandatory (Deferred), Revisions to the Protocol and the DSMP are required.>
Please address the concerns below in a timely manner:
.

1. This study has been deemed <"High Risk, Medium Risk or Low Risk"> and <"greater than minimal risk but has prospect of direct benefit, greater than minimal risk but no prospect of benefit or not greater than minimal risk."> Please ensure that your IRB Protocol matches this information upon IRB submission.

Once the PRC has received your responses to the above questions, we will be happy to review the protocol <upon re-submission (contingent) or at a future meeting (deferred or not approved.)>
Please address these issues as listed above in a response letter with your resubmission. **In your response letter to the PRC, please include the PRC submission number in the Title. If you are submitting revisions to a protocol, please submit tracked change versions. If you do not submit tracked change version of the protocol, it will result in a delay in the review of your trial.** If you do not plan to pursue the approval process with this protocol, please advise the PRMS coordinator.

Sincerely,

James Larner, M.D.
Protocol Review Committee

Cc: <Submitter name>

Appendix C: Template PRC Approval Letter

The Cancer Cente

University of Virginia HEALTH SYSTEM

James Lamer, MD
Director and Chairman

Stacey Williams
PRMS Coordinator

Date

Richard Stevenson, MD
UVA Institutional Review Board for Health Sciences Research
P.O. Box 800483
Charlottesville, VA 22908

Re: PRC # <Insert> "Title"

IRB Submission or IRB # <Insert>

Dear Dr. Stevenson:

As of <Date>, IRB Submission or IRB #<Insert>, titled "<Insert Title>" trial has received full PRC Approval. Please review the following information:

1. PRC Approval has been given for the <Date> version of the Sponsor's protocol and the <Date> version of the IRB Application or IRB Protocol.

Response:

2. This is Phase <I, II, III, IV> or <Non-Therapeutic, Non-UVAInstitutional, UVA Institutional, Pharmaceutical study>.

3. This trial has been deemed "<Low, Medium, High>" risk by the PRC. The Risk ratio assessment is not involving greater than minimal risk, greater than minimal, but it has prospect of direct benefit to patients, greater than minimal risk and no prospect of direct benefits to patients.

4. PI or study team <is required to or is not required to> reports all patient accruals to OnCore on a monthly basis.

5. PI or study team is required to or is not required to report all AE's to IRB, OnCore and sponsor as described in DSMP.

6. The PI is required to or is not required to submit revisions to the PRC.

7. The Responsible Oversight Body is the <UVA Cancer Center DSMC, sponsor identified Medical Monitor or DSMB, or DSMB.>

Please let me know if there are any further questions.

Sincerely,
James Larner, M.D.
Protocol Review Committee

Cc: PI
CRC

Appendix D: PRC Performance Review Letter:

The Cancer Center

University of Virginia HEALTH SYSTEM

<Date>

<PI Name>, <Title>.
Associate Professor
Department of <Department Name>
Box <#>

Re:> November or May> <Year> PRC performance review

Dear Dr<PI Last Name>. :

The PRC will be holding its semi-annual performance review of protocols that have not accrued any patients in the prior six months, or that have not met 45% of their 12-month target over the prior year. Protocols previously designated as "rare disease" will also be reviewed if they have had no accruals in the previous 12 months or previous 36 months. The performance review does not include consented or screened patients, and studies that have been open to accrual less than six months are not included in the review. This semi-annual review is conducted in compliance with the PRC's review and monitoring policy, which was approved and funded by the NCI in the Cancer Center's 2005 CCSG application. Under those criteria, the following protocols are eligible for review:

For review under the six-month non-accrual criteria:

IRB#"					
Opened to Accrual	6-month Accrual	12-month Target	Protocol Target	Accrual To Date	Last Patient Registration

For review under the 45% criteria:

IRB#"					
Opened to Accrual	12-month Accrual	12-month Target	Protocol Target	Accrual To Date	Last Patient Registration

If the review is the first such review for this study, the PI and/or managing office must submit a response in writing with a plan of action to address the lack of accrual to the study. Corrective

action may include but not be limited to a review or revision of the eligibility criteria or re-introduction of the study to potential investigators. If no response is received, the studies will be closed. Studies which are reviewed in two consecutive reviews may be closed.

Your plan for addressing the accrual rates for these protocols will be reviewed at the < Date> meeting of the PRC. Please respond in writing to the PRC Coordinator with your plan. In the interest of time, e-mail is acceptable.

Please contact the PRC coordinator with any questions.

Sincerely,

James M. Larner, M.D.
Chair, Protocol Review Committee

cc: CRC

Appendix E: PRC Performance Review Response Letter:

The Cancer Center

University of Virginia HEALTH SYSTEM

<Date>

<PI Name>, <Title>.
Associate Professor
Department of <Department Name>
Box <#>

Re :< May or November> <Year> PRC performance review

Dear Dr. <PI Last>::

The PRC held its semi-annual performance review on <Date>. As you know, this review was conducted of protocols that have not accrued any patients in the prior six months, or that have not met 45% of their 12-month target over the prior year. Protocols designated "rare disease “were reviewed if there had been no patients registered in the prior 12 months or in the prior 36 months. Protocols that opened in the prior six months were not eligible for review. Accrual was defined as registered patients and did not include screened or consented patients who had not been registered. This semi-annual review was conducted in compliance with the PRC's review and monitoring policy, which was required and approved by the NCI in the Cancer Center's <2011> CCSG application.

Thank you for your response to the PRC performance review. The following protocols were reviewed. PRC responses are as follows each listing:

IRB <#> <Short Name>:

<The Committee has <no objections to, concerns regarding> the protocol(s) listed above remaining open.> <The committee is closing your study due to non-compliance, slow accrual. This study must be closed immediately or within1 month of receipt of this letter.> <However, if enrollment does not improve within 6 months, this trial will be closed to accrual.>

Please contact the PRC coordinator with any questions.

Sincerely,

James M. Larner, M.D.

Chair, Protocol Review Committee

cc: CRC

Appendix F: PRC Roster

The current PRC Roster can be located at the following website at:

http://www.medicine.virginia.edu/research/research-centers/cancer-center/cancer-research/prc/prc-members.html