University of Virginia
Comprehensive Cancer Center

Data and Safety Monitoring Plan
for Clinical Research

Approved: National Cancer Institute

5/29/2024

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1. Introduction

The University of Virginia Comprehensive Cancer Center (UVACCC) has responsibility for overseeing the conduct of cancer-related clinical trials that involve research activities related to cancer. The University of Virginia Comprehensive Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials.

National Institute of Health (NIH) and National Cancer Institute (NCI) policies require that data and safety monitoring plans be in place for all clinical trials that involve an intervention. NIH policy dated June 10, 1998 (http://grants.nih.gov/grants/guide/notice-files/not98-084.html) with additional description issued on June 5, 2000 (at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html) requires that grantees have in place procedures for data and safety monitoring (DSM) of clinical trials. Information for NCI National Clinical Trials Network (NCTN) Groups Data Monitoring Committee Policy (Phase 3 Trials) can be found at http://www.cancer.gov/research/areas/clinical-trials/nctn . Lastly, a guide to the formulation of DSM plans for all phases of cancer clinical trials, in accordance with NIH requirements, can be found at http://www.cancer.gov/research/resources/conducting.

In accordance with the NIH requirements, the UVACCC has developed an Institutional Data and Safety Monitoring Plan (DSMP) that outlines appropriate oversight and monitoring of all cancer- related interventional studies. The purpose of the DSMP is to ensure the safety of participants, the validity of data, and the appropriate process for termination of studies for which significant benefits or risks have been determined or when it appears that the investigation cannot be concluded successfully. All study principal investigators (PIs) will be required to adhere to the plan.

2. Organization and Administration

The UVACCC protocol review and monitoring system (PRMS) has been established to ensure patient safety by coordinating, monitoring and providing oversight for study data and patient safety for all cancer-related studies. This protocol review and monitoring system is comprised of the Institutional Review Boards (IRB), the Protocol Review Committee (PRC), the Data and Safety Monitoring Committee (DSMC), the Office of Clinical Research Quality Assurance program (CC OCR QAP), and the Cancer Center's Clinical Trial Advancement Committee (CTAC).

Institutional IRBs are managed by the Office of the Vice President for Research (VPR) to ensure compliance with federal research regulations. The Office of the VPR also develops policies on conflict of interest and handles investigations on issues of research integrity.

Within the UVACCC, the PRC and the DSMC provide the infrastructure for scientific oversight and monitoring of cancer-related clinical trials. PRC review is a requirement of the National Cancer Institute as part of our Cancer Center designation. The PRC reviews new clinical trial protocols, with an emphasis on investigator-initiated trials and industry-sponsored trials that have not received an NIH or equivalent peer review (e.g. American Cancer Society, Department of Defense, National Science Foundation). National cooperative group trials are not required to have local full-board scientific review, only an expedited PRC chair review as they receive detailed review at the level of the sponsoring group, as well as through the NCI Cancer Therapy Evaluation program (CTEP).
The DSMC provides oversight of the conduct of all ongoing institutional clinical

trials that have been approved by the PRC and that are not monitored by an approved external board, organization or agency.
The CC OCR QAP is the audit arm of the DSMC. The CTAC provides internal oversight for the PRC and DSMC.

The key components of each entity are described below. A schema of the organizational structure is given in Appendix A.

Ultimately, it is the responsibility of the local study principal investigator (PI) and the co-investigators to provide continual monitoring of their clinical trial. In this role, the local PI receives support from the PRMS in overseeing the safety and progress of the study.

2.1. Institutional Review Board (IRB)

There are two institutional IRBs responsible for the protection of human subjects in research at the University of Virginia. The IRB-HSR is the IRB responsible for reviewing all human subject research involving biomedical procedures throughout the University of Virginia. The IRB for the Social and Behavioral Sciences (IRB-SBS) at the University of Virginia is the IRB responsible for reviewing all non-medical social, behavioral or educational human research for compliance with federal regulations. Review of research is required for all research conducted by faculty, staff and students of the University of Virginia. All activities involving human subject research must be reviewed and approved by the appropriate IRB prior to implementation. Currently, the research protocols involving cancer patients fall under the domain of either the IRB-HSR, commercial IRBs or NCI-CIRB.

A small number of protocols submitted to the IRB for the Social and Behavioral Sciences (IRB-SBS) and in a similar manner to the IRB-HSR, are required to be reviewed first by the PRC before submission to the IRB-SBS. These studies receive oversight by the PRC and are not monitored or audited by the DSMC or the OCR QAP.

According to UVA IRB-HSR policy, every protocol submission is required to include a Data and Safety Monitoring Plan (DSMP). This plan should complement any plans developed by study sponsors (where applicable) and must conform to one of the templates developed by the IRB. The purpose of the DSMP is to ensure that each clinical study has a system for appropriate oversight and monitoring, according to the risk encountered by the participants, to ensure the safety of the participants and the validity and integrity of the data.

2.1.1. IRB Requires PRC Approval

The IRB does not accept cancer-related protocols for review without prior PRC approval, except for NCI cooperative group trials and other protocols that do not require PRC review (see section 2.2). The PRC indicates its approval by issuing an approval letter that includes the following information: PRC number; oversight responsibility; risk level; and, where applicable, monitoring frequency. NCI NCTN trials are exempt from further scientific review (please see section 2.2 for more information on PRC exemptions) but do require administrative review for competition. The PRC Coordinator receives IRB agendas and minutes in order to ensure that no protocol is submitted for IRB review without the appropriate PRC review.

2.1.2. IRB Requires COI Approval

The University of Virginia Vice President for Research and Graduate Studies appoints the Conflict of Interest (COI) Committee for management of institutional financial interests in research. The COI Committee is made up of two faculty members, one senior administrator, and various non-affiliated community members, representing diversity of expertise needed to adequately review potential institutional conflicts of interest. This committee reviews cases in which an institutional official or the institution itself holds a significant financial interest that may affect or appear to affect the results of a research project. The committee determines whether the research can be conducted at the University and whether any resulting management strategies are required. Management strategies are developed and implemented to address conflicts of interest and to assure that the institution may satisfy any research obligations in an objective manner and to avoid and/or mitigate concerns of bias. Approved management plans are forwarded to the IRB by the COI Committee to communicate any requirements for disclosure in informed consent documents. The COI Committee may recommend that the research may not be conducted at the University of Virginia. The UVA School of Medicine (SOM) Policy on Conflict of Interest with details of the composition and responsibilities of the COI Committee can be found at: https://uvapolicy.virginia.edu/policy/RES-005

The SOM COI policy is based upon the State and Local Government Conflict of Interests Act (Title 2.2, Chapter 31 of the Code of Virginia, for more information visit virginia.gov) and the Governor's Executive Order 16 (2006).

2.2. Protocol Review Committee (PRC)

The Protocol Review Committee (PRC), the institutional peer-review system for all cancer-related research, is responsible for:

a) Reviewing scientific merit;
b) Mediating competing studies by requiring an agreed upon institutional prioritization plan and patient availability;
c) Closely monitoring clinical trial progress and rules for termination of studies in the Cancer Center based upon accrual and continued scientific relevance

2.2.1. PRC Membership

The Protocol Review Committee Chair and Co-chair are appointed by the Director of the Cancer Center. The members of the committee are appointed by PRC Chair(s). Members are selected to provide a group with diverse expertise. The Chair may appoint additional members on an ad hoc basis. PRC membership is listed at: https://med.virginia.edu/cancer-research/cancer-clinical-research-support/protocol-review-commitee/protocol-review-procedures/

2.2.2. Confidentiality Procedures

No communication, either written or verbal, of the deliberations or recommendations of the PRC will be made outside of the PRC except as provided for in this policy. All committee members and guests at PRC meetings are required to sign a confidentiality statement. If issues are identified at the meetings, PRC deliberation/recommendations will be discussed with the IRB directly and with the Cancer Center Senior Leadership through the

CTAC. Outcome results are strictly confidential and must not be divulged to any non-member of the PRC.

Principal investigators and/or study team members are welcome to attend PRC meetings after obtaining permission from the Chair(s). They can help explain the study and answer questions from the committee. After the PI has answered questions, she/he must leave the room for final Committee deliberations and voting. The PRC has the authority to approve, require modifications, or reject a protocol.

2.2.3. Conflict of Interest

PRC members are subject to the Commonwealth of Virginia Standards of Conduct found at: http://www.dhrm.virginia.gov/docs/default-source/hrpolicy/pol1_60.pdf. Individuals invited to serve on the PRC will disclose any potential conflicts of interest, whether real or perceived, to the members of the PRC and the appropriate UVACC official(s), in accordance with the UVA SOM Policy on Conflict of Interest and Conflict of Commitment (https://uvapolicy.virginia.edu/policy/RES-005)
Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Page II-12, and 45 CFR Part 94. Potential conflicts that develop during a member's tenure on the PRC must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in the PRC are made in accordance with the institution's policies. All committee members are required to disclose any conflicts of interest and sign a conflict of interest statement.

In a case where the PRC Chair has a conflict of interest, the Co-chair will assume leadership of the committee. In cases when both Chair and Co-chair have conflict of interest one of the physicians on the committee will assume leadership responsibility.

2.2.4 PRC Review of Scientific Merit

1. Interventional Trials:

a. **All therapeutic trials** require PRC full board review, except** NCI-sponsored trials, externally-peer reviewed trials (such as those described under Data Table 4 in https://cancercenters.cancer.gov/GrantsFunding/DataGuide) or multi-site Investigator initiated trials that have received PRC approval from another NCI-designated PRMS which may be reviewed in an expedited manner.
b. **Non-therapeutic interventional trials** (i.e. prevention, supportive care, screening, early detection, diagnostic studies) usually require PRC full board review, but if deemed appropriate by the Chair a non-therapeutic interventional trial may be reviewed solely by the Chair of the PRC or his designee. Examples of such trials include blood draws, tissue samples from biopsies, and imaging.

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

2. Non-interventional protocols
a. Observational, correlative studies are reviewed solely by the Chair of the PRC or his designee.

b. Database protocols and tissue banking protocols for prospective resources undergo Chair review as well.

3. **Trials Exempt from PRC review**:

- Protocols involving healthy human volunteers
- Retrospective chart review.
- Single patient INDs
- Epidemiology protocols
- Protocols that study discarded tissue and correlate with chart review
- Protocols involving cancer patients that do not have a cancer focus (i.e. cancer is not an inclusion criterion).

2.2.4.1 PRC Protocol Review Process for Therapeutic and Interventional Non-therapeutic Protocols

Each protocol undergoes a two-stage review:
1. At the Disease Team level where scientific and logistical questions are answered via a Protocol Submission Form. This helps the disease team identify and prioritize trials they want to participate in based on disease relevance and patient population needs. Protocol discussions are pre-planned and allow for the team to read through the protocol prior to discussion at the planned meeting.
2. Once approved by the Disease team, the protocol documents along with the Protocol Submission Form are submitted to the PRC.
PIs submit interventional therapeutic and interventional non-therapeutic protocols as described in section 2.2.4 to the PRC. These studies receive review by the PRC full board, consisting of at least two medical reviewers, one biostatistics reviewer, and one data and safety monitoring plan (DSMP) reviewer. If the protocol utilizes an investigational agent, a review is obtained from the clinical pharmacist. The PRC may seek reviews from *ad hoc* reviewers when needed if the Committee members are not qualified to adequately review the proposed study.

For each new interventional therapeutic and non-therapeutic protocol submitted to the PRC, the principal investigator is required to submit the following documents:

- Study Protocol
- PRC Submission Form
- Investigator Drug Brochure (if applicable)
- Investigator Device Brochure (if applicable)

The PRC reviewers, who have an expertise in medicine, pharmacy, biostatistics, population health, data management, and DSMP, examine the following areas during the PRC review process:

1. Scientific merit, with an emphasis on the following:
    - Completeness of background information to support study rationale
    - Appropriateness of objectives for the patient population
    - Clarity and appropriateness of eligibility criteria
    - Suitability of methods (including appropriate blinding/masking procedure and/or appropriate randomization) to achieve the stated objectives
    - Feasibility of completing the trial (accrual goals, conflicting protocols, obstacles to

successful implementation)
- Risk category and risk-benefit ratio

2. Pharmacy criteria
   - Dosing administration and treatment schedule
   - Inclusion of expected side effects
   - Management of adverse effects including dose modifications if necessary
   - Inclusion of all prohibited and pre-medications

3. Biostatistical analysis
   - Inclusion of stopping rules and interim analyses
   - Appropriateness of sample size and statistical analysis method
   - For industry-sponsored therapeutic protocols, does the statistical design and sample size fit within industry standards and/or FDA standards for clinical trials?
4. Data and Safety Monitoring Plan
   - Ensuring the protocol and DSMP correlate
   - Completeness of Data Safety Monitoring Plan

A minimum quorum for a face-to-face committee meeting includes 4 physician members (or translational scientist), PRC Chair (or designee), a minimum of 2 other non-physician members, and a total of at least 9 members.
In cases with unresolved concerns, votes must be received from a minimum of 4 physician (or translational science) members and from at least 1 member from each of the other categories (pharmacy, data and safety monitoring plan and statistics). Based on the review, the Committee issues one of five findings on the protocol:

1. Approved as written;
2. Approved with suggestions;
3. Approvable with clarifications (minor clarifications or revisions required; submitted revisions may be approved by Chair or his designee);
4. Deferred(major concerns, requiring review at subsequent PRC meeting post resubmission with revisions)
5. Disapproved. (not approvable as written)

Following each meeting, the Chair, with the assistance of the PRC Coordinator, outlines a summary statement of issues that must be addressed prior to PRC approval. When revisions and/or responses are required, study investigator is expected to respond within 30 days from date of initial PRC review. If the investigator submits a response to the PRC within six months, the resolved issues can be administratively approved. If the response returns after six months have elapsed, the protocol must undergo another full Committee review. Before PRC approval can be granted, PIs revisions and responses must address all issues raised in the previous review. If PRC reviewers require mandatory revision(s), PIs must submit an updated protocol or DSMP with tracked changes. Once the revised protocol is submitted to the PRC, a committee vote is conducted to determine approval vs disapproval based upon majority of responses.

For protocols that are approvable with clarifications and PI revisions or responses do not fully address the original reviewer's concerns, the committee will vote on how to proceed. PRC voting can be conducted either in person or electronically. Each voting individual may vote to approve, disapprove or abstain.
The PRC Coordinator notifies the PI when approval is granted, and issues an approval letter.

Once a protocol has undergone full board review, subsequent revisions 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.
Modifications for NCI cooperative group and other peer-reviewed protocols do not require PRC approval.

2.2.4.2 PRC Protocol Review Process for Non-interventional Protocols

For each new non-interventional protocol submitted to the PRC, the principal investigator is required to submit the following:

- Study Protocol
- PRC submission form

These trials are eligible for PRC review by the Chair only or his designee, utilizing the same review criteria followed for full board reviews. Trials appropriate for expedited review by the Chair only are submitted and reviewed independently of the monthly PRC submission deadlines for full Committee review. Protocol reviews by the Chair only or his designee are completed within 14 days of submission, a timeline which is comparable to that for full board review.

2.2.5 Competition review

The PRC is responsible for assessing competition across the clinical trials portfolio, including national cooperative group protocols. PRC review takes into consideration whether a protocol competes with existing or pending protocols for a particular participant pool. The Committee assesses potential competition by comparing eligibility criteria for similar protocols by disease site. Investigators provide statements on competition with other active protocols, and the PRC reviews the statements.

The PRC may not approve protocols that directly compete with an open or pending institutional or NCI-sponsored trial. If direct competition exists between or among studies, the PRC assigns priority as follows:

1. UVA Investigator-initiated trials;
2. NCI NCTN or ETCTN group protocols
3. non-UVA investigator-initiated trials;
4. Industry-sponsored protocols.

The Cancer Center encourages teams to submit successive protocols for a patient population to replace a protocol that is close to completion or likely to close. The PRC seeks input from the PI or study team before making decisions to address competition.

2.2.6 PRC Protocol Monitoring

Accrual monitoring: 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.
Accrual monitoring begins when a trial opens to accrual and ends when it's closed to accrual. Accrual is reviewed semi-annually at PRC meetings in May and November. PRC may close non-accruing trials and a letter with this recommendation is sent to the PI. Protocols that use specimens that cannot be linked to patient identifiers are exempt from accrual reporting.

Safety monitoring: It is the responsibility of the PRC to review and respond to reports and safety issues brought to their attention by 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. The PRC has the authority to close trials to patient accrual should the risk to patients be deemed excessive, if data and safety monitoring is unsatisfactory, or if accrual to the study is too low. On DSMC recommendation, the PRC temporarily closes protocols to accrual until issues or concerns are addressed. The DSMC may request that a protocol be closed permanently.

Criteria for closure of the protocol by PRC include but are not limited to the following:

- Safety concerns and Adverse Event (AE)/Serious Adverse Event (SAE) reporting
- Non-compliance with institutional requirements, including patient registration and data reporting
- Non-compliance with the protocol-specific data and safety monitoring plan
- Semi-annual accrual falling below 45% of the estimated rate

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 team. If the response from the study team is satisfactory PRC may reopen study to accrual.

Accrual data is entered monthly into OnCore. Using this information, the PRC Coordinator provides a report in May and November on under-accruing trials that meet the performance review criteria established by the PRC. At these meetings, the PRC reviews:
(1) Studies that have been open for at least six months that have not accrued any registered patients and
(2) Studies that have been accruing at less than 45% of the estimated accrual rate over the trailing six-month period.
The PRC Coordinator sends letters to the PI and study team of each non-accruing trial that meets performance review criteria prior to the May and November meetings.

If accrual does not meet the above performance criteria, PIs must respond in writing with a corrective plan of action to address accrual issues. The study's first review requires a response within 14 days from the PI and/or managing office with a plan of action addressing the lack of accrual to the study.
Corrective action may include, but is not limited to:
a) Review or revision of the eligibility criteria;
b) Revision of target accrual numbers and
c) Re-introduction of the study to potential investigators.

The Committee reviews the responses at the May and November PRC meetings. These reviews do not include consented or screened patients. The review does not include studies that have been open to accrual less than six months that do not register or enroll. If no response is received from the study PI, the study is closed until a response is received and reviewed by the PRC. Studies which have three consecutive unsatisfactory reviews will be closed. Studies for which accrual remains an issue on consecutive reviews may be closed prior to completion of the study.

2.2.7. PRC Risk Classification

The PRC assigns a risk classification level that dictates the level of monitoring by the DSMC as requested by the IRB-HSR for each study. The following are general guidelines for risk classification; however the PRC has full discretion when determining the risk classification for each study.

- 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)

The PRC reviews revisions of all UVA investigator-initiated protocols. If a revision of an investigator-initiated protocol changes the protocol's design, the risk level may be reassessed, if appropriate.

2.3 Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) is charged with oversight of UVA investigator-initiated cancer-related therapeutic or non-therapeutic interventional trials. The UVACCC DSMC acts as both an oversight body as well as a resource for cancer center investigators to ensure safe conduct of all investigator-initiated trials.
NOTE: Non-interventional studies and studies exempt from PRC review are not monitored by the DSMC.

For each protocol, a DSMC team of a physician and a non-physician serve as primary monitors for the protocol. Each team member receives copies of the full protocol and the most current version of the informed consent documents. DSMC summary reports are submitted to the committee members the week prior to the meeting. Upon initial review, the primary reviewers may request more details about adverse events (AEs) such as copies of adverse event forms submitted to the IRB-HSR or additional information from the PI. The monitoring team discusses their findings during the DSMC meeting.

2.3.1 DSMC Membership

- The DSMC consists of at least 6 members with varied expertise from oncology subspecialties and clinical trials experience.

- The DSMC membership is multidisciplinary. The committee includes the following representatives: physician members of the Cancer Center, biostatistician, pharmacists, nurses and study coordinators. PRC members also serve on the DSMC to promote communication between the two committees.

- Any member of the committee may nominate new members to the DSMC and after qualifications are reviewed and approved by the committee, the Chair will appoint the new member.

- Members serve on the DSMC until they choose to resign or are replaced by the Chair or Cancer Center Director.

- DSMC members should have familiarity with IRB policies and procedures including, but not limited to, reporting policies of the IRB, Office of Human Research Protection (OHRP), Food and Drug Administration (FDA), and the NIH for adverse events, serious adverse events, unanticipated problems, protocol deviations, and other clinical research related reporting obligations.

- DSMC members must be able to attend monthly DSMC meetings to ensure membership quorum.

If requested by the DSMC Chair(s), the PRC Chair(s) may assist in identifying qualified members to join the DSMC who are free of any conflict of interest.

The current DSMC roster is located at: https://med.virginia.edu/cancer-research/cancer-clinical-research-support/protocol-review-commitee/data-safety-monitoring-committee-dsmc/

2.3.2 Confidentiality Procedures

No communication, either written or verbal, of the deliberations or recommendations of the DSMC are made outside of the DSMC except as provided for in this policy. If issues are identified at the meetings, DSMC deliberation/recommendations are discussed with PRC, IRB, Cancer Center senior leadership in the CTAC, and CC OCR QAP. Outcome results are strictly confidential and must not be divulged to any non- member of the DSMC. Each member of the DSMC, including non-voting members, must sign a statement of confidentiality. Guests attending meetings must also sign a statement of confidentiality.

2.3.3 Conflict of Interest

DSMC members are subject to the Commonwealth of Virginia Standards of Conduct found at: http://www.dhrm.virginia.gov/docs/default-source/hrpolicy/pol1_60.pdf. Individuals invited to serve on the DSMC as either voting or non-voting members will disclose any potential conflicts of interest, whether real or perceived, to the members of the DSMC and PRC and the appropriate UVACCC official(s), in accordance with in accordance with the UVa SOM Policy on Conflict of Interest and Conflict of Commitment https://uvapolicy.virginia.edu/policy/RES-005.Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Page II-12, and 45 CFR Part 94. Potential conflicts that develop during a member's tenure on a DSMC must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in a DSMC are made in accordance with the institution's policies. All committee members are required to disclose any conflicts of interest and sign a conflict of interest statement.

In a case where the DSMC chair has a conflict of interest, the Co-chair will assume leadership of the committee. If the chair and co-chair are unavailable, one of the senior physicians on the committee will assume responsibility.

2.3.4 DSMC Meetings

The DSMC meets either in person or electronically monthly. A week prior to the DSMC meeting, the DSMC Coordinator emails the committee members updated information about protocols that require review.

The DSMC meets in closed session to discuss the general conduct of the trial and all outcome results, including toxicities and adverse events, to develop recommendations, and take votes as necessary. In order to have a quorum of 5, DSMC Chair with at least two physicians and two non- physicians must be present at the meeting.

2.3.5 DSMC Responsibilities

At the meetings, DSMC members review and discuss the following:

- Review data (including blinded data) over the course of the trial relating to efficacy, recruitment and accrual, randomization, compliance, retention, protocol adherence, trial's operating procedures, forms completion, intervention effects, and subject safety.
- Identify problems relating to safety over the course of the study. Inform study PI via written report who in turn will ensure that all clinical collaborative site PIs receive this report.
- Identify needs for additional data relevant to safety issues and request these data from the study investigators.
- Propose appropriate analyses and periodically review developing data on safety endpoints.
- At each meeting, consider the rationale for continuation of the study, with respect to, protocol adherence and compliance, data management, safety issues, outcome data, if relevant, and make a recommendation for or against continuation of the trial.
- Provide documentation to PIs when issues are identified, CC OCR QAP audit has occurred, or at the time of the IRB request for annual renewal.
- If there is more than one clinical site, the study PI is responsible for sending the reports to individual site PIs, who in turn are required to distribute the report to their local IRBs, as detailed in the NIH "Guidance on Reporting Adverse Events to Institutional Review Boards for NIH Supported Multicenter Clinical Trials" (NIH Guide for Grants and Contracts, June 11, 1999).

2.3.6 DSMC Monitoring

Monitoring by the DSMC begins at the time the first subject is enrolled to the study. Semi-annual data audits are required for all High-risk studies and annual data audits are required for Medium- and Low-risk studies. Monitoring by the DSMC ends 30 days after the last active patient completes protocol treatment and the study is closed to enrollment, unless additional monitoring is deemed necessary by the Committee, PI, or IRB-HSR.

A determination of the degree of monitoring by the UVACCC DSMC is based on the risk and the sponsor of the study as follows:

- *NIH*: any protocol sponsored by an NIH-supported cooperative group or consortium will not require monitoring by the DSMC. Any clinical trial that is funded by the NIH (e.g. R01/R21/P01), and is not managed through a supported cooperative group or consortium must have a DSMP with monitoring by the DSMC or an external Data and Safety Monitoring Board (DSMB).

- *Industry*: any clinical trial conceived and initiated by pharmaceutical industry sponsors with subsequent CC participation are monitored by the company holding the IND and will require DSMPs that have been reviewed and approved by the PRC and IRB. DSMC monitoring will not be required.

- *Institutional UVA investigator-initiated**: any institutional, investigator-initiated therapeutic or non-therapeutic trial will require a DSMP and monitoring by the

DSMC or an external DSMB.

- *Multi-institutional UVA investigator-initiated**: any multi-institutional, investigator- initiated trial will require a DSMP and monitoring by the DSMC or an external DSMB.

- *Multi-institutional non-UVA investigator-initiated*: any multi-institutional trial conceived and initiated by another institution with subsequent UVA CCC participation will require DSMPs that have been reviewed and approved by the PRC and IRB. DSMC monitoring will not be required.

*-Except Non-interventional and those deemed exempt by PRC

2.3.7 DSMC Recommendations

The DSMC recommendations should be based on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from other related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

All open therapeutic investigator-initiated protocols are reviewed on a monthly basis. Issues that require action will be reported to the PRC. Any DSMC recommendations will be documented in monthly meeting minutes. If necessary, the committee will send a letter to the PI, PRC and the IRB outlining the DSMC's recommendation. The PRC will review the recommendations from the DSMC and take appropriate action. The DSMC also has the authority to report directly to the IRB any serious issues (e.g., clinical trial conduct, compliance with adverse event reporting guidelines, or major violations noted in audits).

Issues that would lead to a recommendation to close accrual include, but are not limited to, the following:

- A higher than anticipated number of unexpected life-threatening or fatal adverse events with benchmarks defined in the DSMP
- Major deviations noted in consecutive audits
- Inadequate monitoring by the DSMB, as evidenced by lack of monitoring reports from the DSMB to the DSMC

2.4 Office of Clinical Research QAP: DSMC audits and internal monitoring

The Cancer Center's Office of Clinical Research Quality Assurance program has been tasked with following objectives:

- To ensure compliance with federal, state, local and institutional regulations and guidelines
- To uphold the rights and well-being of clinical research participants, as well as the quality and integrity of clinical research
- To offer tailored education and research support that meets the needs of clinical researchers
- To identify areas of strength and areas needing improvement in research policies and practice

This program is utilized to conduct both compliance audits for the Cancer Center DSMC

as well as ongoing internal monitoring of trials.
Standard Operating Procedures (SOPs) for the OCR QAP can be found here .

2.4.1 Procedures for DSMC regulated audits

The audit procedure is a formal, broad, source document review of any investigator initiated/institutional trial not otherwise audited by an external agency. The purpose of audits is to ensure that documentation of clinical research studies is of the highest quality, verify protocol adherence, and ensure that all Federal and local rules concerning clinical research are being fulfilled.

The frequency of post approval auditing of studies monitored by the CC DSMC depends upon the risk (High, Medium, Low, or PRC review not required) assigned at the time of the initial review of the protocol by the PRC.

- Semi-annual auditing is required for all High-risk studies and
- Annual auditing for Medium- and Low-risk studies.
- For high-risk studies, if findings are satisfactory after two consecutive reviews, protocols will be audited once a year. Any time findings are unsatisfactory, reaudits will occur within 3-4 months and auditing will return to the original schedule.

Typically, a study will be triggered for an audit once 3 patients have been registered in OnCore.
For studies categorized as high-risk, this audit is triggered once 1 patient has been registered in OnCore.

Any significant revision of the protocol may result in a risk reassessment if deemed appropriate by the PRC Co-Chairs and consequently may require change in audit frequency.

The DSMC biostatisticians will be responsible for randomly selecting the cases for audit. Audits will include review of all patient consent forms, as well as 10% or a minimum of 3 or a maximum of 10 complete records. The audit will also verify the accuracy of the study data and assure the timely and complete reporting of safety data. Compliance with the protocol, Good Clinical Practices (GCP) guidelines, and IRB-HSR policy will be assessed in the audit. Protocols utilizing study drugs will have drug accountability reviewed.
Written reports of the audit are reviewed by the DSMC, which through this process, provides for quality assurance activities for cancer-related studies.

2.4.2 OCR Internal monitoring

In order to facilitate and implement an “audit ready” environment for all UVACCC clinical trials using non- punitive reviews in combination with education, the CC OCR QAP will also conduct ongoing internal monitoring. Ongoing OCR monitoring of a CC clinical trial would be initiated for the following indications but not limited to the following:

1. Workload and FTEs are unbalanced due to change in staff
    a. Number of open protocols, active patients, accrual vs. amount of staff
2. New CRCs will receive an audit 6 months from hire date upon request from management.
3. OCR Education Coordinator has recognized a significant number of protocol violations that involve any or all of the following safety categories:
    a. Consenting
    b. Drug Administration/Dosing

c. AE reporting
d. OnCore reporting
e. CRF completion

4. At the request of a study team member or OCR management

2.5 Clinical Trial Advancement Committee (CTAC)

The Clinical Trial Advancement Committee (CTAC) for the UVA Cancer Center's Office of Clinical Research (OCR) is responsible for successfully developing, promoting, implementing, and achieving the Cancer Center's strategic plan for clinical research. The CTAC provides operational direction to the OCR, reviews and approves the policies and procedures, minutes, and correspondence of the PRC and the DSMC, and participates in decisions regarding all aspects of planning and evaluation that affect services offered. The CTAC is comprised of PRC, DSMC, and OCR leadership as well as other Cancer Center senior leaders from different oncology subspecialty disciplines.

3. Investigator Responsibilities

Ultimately, it is the responsibility of the study PI to provide continual monitoring of his or her trial and to ensure that the DSMP is followed. The PI is responsible for ensuring that all data required for oversight are accurately reported to the internal or external monitoring committee as required and all adverse events are reported according to protocol guidelines and institutional requirements.

Investigator responsibilities include:

- Develop a DSMP
- Enter data into OnCore.
- Maintain all study-related regulatory documents
- Report all AE's
- Obtain confirmation by an independent reader of all complete responses observed in subjects enrolled on treatment trials
- Verify frequency and report information required of PI for the DSMC (or external monitoring board) and IRB-HSR
- Respond and take appropriate action to issues raised by the DSMC (or external monitoring board), PRC or IRB-HSR
- If a study is an IND or IDE trial receiving federal funds, PI must inform the awarding institute of significant communications from FDA, in accordance with NIH policy released 9/22/00 entitled "Notice To NIH Grantees/Contractors Regarding Letters or Notices From The Food And Drug Administration (FDA)."
- If the study is an NCI-sponsored trial, per NCI requirements, the PI must inform the NCI Program Director responsible for funding the trial of any communication affecting the trial status (e.g., trial suspension or closure).

3.1 Data and Safety Monitoring Plan Requirements

3.1.1 Adverse Event Reporting Guidelines

The recommended default reporting guidelines for UVA investigator-initiated studies that will be monitored by the Cancer Center DSMC are given in Appendix B, Tables A, B, C. Requests to deviate from these requirements must be submitted to the DSMC for approval. The guidelines are based upon the Cancer Therapy Evaluation Program (CTEP) reporting

requirements (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf).

It is the responsibility of the PI (or designee) to notify the sponsor, NIH/NCI, FDA or other agencies of serious adverse events as required in the protocol.

If the UVACCC is acting as the coordinating center for multi-institutional studies, it is the responsibility of the PI (or designee) to submit all adverse events from the participating sites that meet the reporting requirements to the FDA, IRB-HSR and DSMC. In addition, for IND studies, it is the responsibility of the PI (or designee) to ensure that all adverse events meeting expedited reporting requirements are submitted to the appropriate IRBs per their guidelines.

Adverse Event (AE) reporting requirements begin with what is written in the protocol and the risk level of the study. A list of specific AEs to be addressed at every evaluation interval is written in each protocol. All AEs on this list are reported as directed in the protocol.

Generally, this will be a very tightly circumscribed list of lab values and clinical signs and symptoms.

Any reported adverse event is graded using the specific AE terms listed in the appropriate version of the Common Terminology Criteria for Adverse Events (CTCAE) for any given IRB-approved protocol. Reporting requirements always include routine reporting and expedited reporting according to the IRB approved protocol. The CTCAE document is available as a reference for grading AEs at: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

For studies monitored by the DSMC, all routine reporting of AEs is done by entering AEs into OnCore within the time frame specified in the protocol.

3.1.2. Investigator-initiated Multi-center Trials

When more than one trial center is involved in a UVACCC investigator-initiated clinical trial, the PI must clearly identify the UVACCC as the coordinating center in the protocol and define the responsibilities of all affiliate centers. PIs sponsoring multi-center UVACCC investigator- initiated studies must identify a sponsor liaison to coordinate trial logistics and provide oversight management of each affiliate site. The liaison (or designee) will be responsible for providing affiliates with protocol amendments, study-specific SOPs, coordination of data capture, monitoring data flow and quality, the reporting and tracking of AEs to the appropriate internal monitoring bodies (DSMC, IRB-HSR). Also, serious AEs from all affiliate sites will be reported to their respective IRBs following applicable policies and procedures.

Unless an alternate monitoring plan has been approved by the PRC, all sites participating in UVACCC investigator-initiated trials are expected to comply with this DSMP. As such, all sites will use the UVACCC-created CRFs/eCRFs designed for the study. All data are entered into OnCore or Advarra EDC or REDCap as pre-determined during protocol development. The study liaison will communicate or distribute adverse event updates to all participating centers by either scheduled phone conferences or an electronic format. Reports of adverse events to each local IRB will be carried out per the individual institutions policy. Reporting to the DSMC will be followed as provided in the associated risk level protocol plan (Appendix B, Table A, B, C). Adverse events that require reporting to regulatory agencies will be completed as required by good clinical practice, and local

policies.

Data are monitored by the PRC and reviewed by DSMC as described in this plan. Affiliate clinical and regulatory data are included in the auditing program. When an affiliate case is randomly selected for audit, the site is informed of this and is expected to submit all source documents for inclusion in the audit. In addition, regulatory documents and pharmacy logs must also be submitted for inspection. Sites are expected to comply with all requests of the PRC and DSMC.

The UVACCC DSMC will be noted in the protocol as the oversight entity of record. If there are additional oversight entities at any of the affiliate centers, the protocol should identify the process of information distribution to the additional oversight entities as applicable.

3.1.3. Independent Image Review

The overall PI of the UVA investigator-initiated trial is required to have all complete responses (CR) observed on-study confirmed by independent analysis prior to any public presentation or publication of study results. The independent analysis must be performed by at least two qualified readers who are not investigator(s) on the trial. The results of the independent image analysis will be provided to the DSMC upon completion of the independent read.

3.1.4 Procedures for External Audits

The PI for a multi-institutional UVA investigator-initiated trial is required to have an audit mechanism in place for all non-UVA affiliate sites and this should be identified in the protocol. The PI is responsible for timely reporting of audit results from these sites to all appropriate monitoring bodies. At a minimum, audits should occur per the guidelines listed in the internal audit section. These sites will be held to the same requirements as UVA. Please refer to the Code of Federal Regulations (CFR) (http://www.gpoaccess.gov/cfr/) and The International Conference on Harmonization (ICH) Guidance Documents (http://www.fda.gov/regulatoryinformation/guidances/ucm122049.htm) for further guidance related to documenting conduct of studies from pre-study planning through study completion.

3.1.5 Audit Findings

Internal Reporting: In the event of unsatisfactory audit findings, audit report summaries, or DSMC final recommendations concerning re-review, study suspension or corrective plans will be sent to the PI, PRC and IRB-HSR. If serious deficiencies are identified, the audit report will contain a corrective action plan to establish goals for compliance and a timeframe for meeting the goals. If compliance is not secured within the specified timeframe, the trial may be suspended or terminated. Any DSMC recommendations regarding accrual review or recommendations for PRC action including study suspension or re-opening will also be sent to the PRC.

A follow-up audit/review will be conducted and a report outlining completion of corrections and compliance with corrective actions, if applicable. This report will also include any revisions to previously identified deficiencies, if appropriate. The follow-up report will be copied to the PI, PRC, IRB-HSR and any agency/regulatory bodies who received the initial audit results/report.

4. Recommendations of Protocol Termination

The PRC and the IRB-HSR have the authority to suspend or terminate a study. The decisions may occur in conjunction with each other or separately.

Grounds for recommendation of suspension or termination of a protocol by the DSMC include, but are not limited to, stopping rule violations or major violations in the conduct of the study that result in an unacceptable audit rating. PIs may appeal to the PRC and DSMC to reopen a study by submission of a corrective action plan and by attending the PRC and DSMC meeting at which the plan will be reviewed and discussed.

The IRB-HSR is authorized (45 CFR 46.113) to suspend or terminate a study at any time if, in its opinion, the risks of further experimentation are prohibitive, or failure to comply with the terms of approval become obvious. These IRB-HSR decisions are likewise subject to appeal.

The decision to recommend suspension or termination of a protocol is carefully considered and takes into account whether corrective actions requested at previous reviews were implemented. If the decision is made to recommend suspension or termination of a protocol, the recommendation will be made in a letter to the PI. A copy of the letter will be sent simultaneously to the chair of the IRB-HSR and the PRC.

The IRB is responsible for reporting any IRB suspensions or closures to enrollment to OHRP, FDA (if applicable) and to any Department of Health and Human Services (DHHS) funding source including NIH and NCI. The study team is copied on those letters. In cases where a trial is funded by an NCI grant, closure of the trial must be reported to the NCI grant program director responsible for the grant.

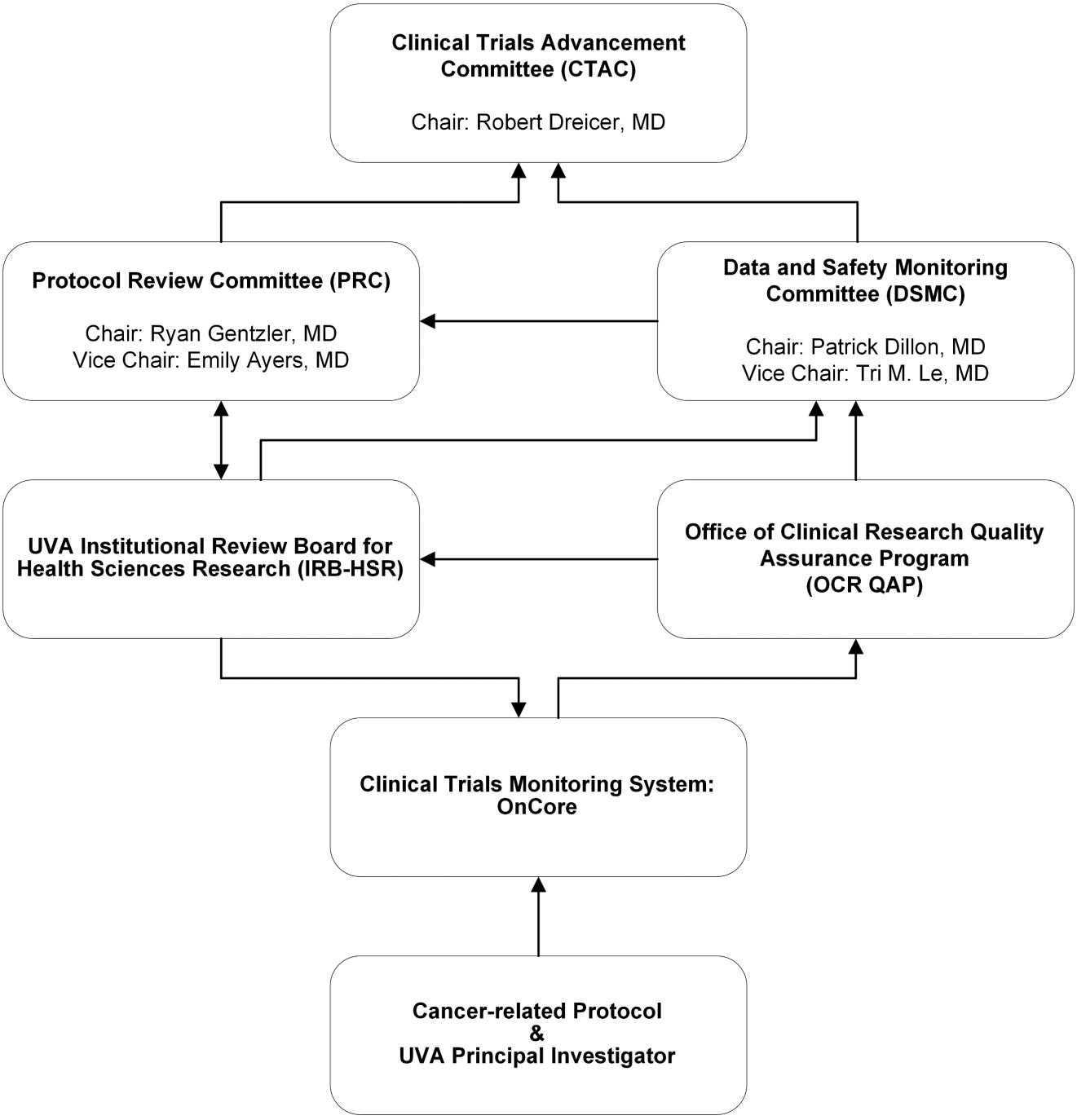
When any of the monitoring bodies suspends enrollment or closes a study for whatever reason, the study team is responsible for notification of all investigators involved with the study at UVACCC and any external sites, the IRB, the sponsor and any funding agency as applicable. Written documentation of this notification by the PI will be forwarded to the DSMC and PRC for filing with other study-related regulatory documentation.

5. Summary

UVACCC is responsible for the support of this institutional plan and accomplishment of its goals. Enhanced processes for data and safety monitoring continue to evolve with focus on high-risk trials as our first priority. Standard operating procedures are being revised and expanded to delineate more fully the necessary responsibilities and activities required to best assure safety, compliance, and reliability of data. At the same time, measures are being considered and implemented to support our faculty and staff in this demanding research environment. The UVACCC is committed to continued improvement of processes that will ensure that clinical cancer research is conducted in the safest and most productive manner possible.

Appendix A

University of Virginia
Comprehensive Cancer Center
Data and Safety Monitoring Organizational Structure



Appendix B

DSMP Template Elements in IRB Protocol Builder

Cancer Center Protocol Review Committee (PRC) Requirements

1. **Designate type of study** *Check only one*

CHECK ONE	TYPE of SPONSOR	Oversight by CC DSMC?	External DSMB Required?	Additional Requirements
	Cooperative Group	No	*If determined by NIH or IRB*	*Enrollment/ accrual information must be submitted to OnCore.* **
	Industry sponsored	No	*If determined by sponsor or IRB*	• *Enrollment/ accrual information must be submitted to OnCore* **
	UVA Investigator Initiated- Single site at UVA	Yes*	*If determined by PRC, NIH or IRB*	• *Enrollment/ accrual information must be submitted to OnCore* **
	UVA Investigator Initiated (Multi-site)	Yes*	*Yes if: Phase III- Medium or High Risk; or determined by PRC, NIH or IRB*	• *Enrollment/ accrual information must be submitted to OnCore* **
	Non- UVA Investigator Initiated (Multi-site)	No	*IRB to determine*	• *Enrollment/ accrual information must be submitted to OnCore* **

**Oversight required by either CC DSMC or an External Board. To be determined by Cancer Center PRC. Studies exempt from PRC review do not require oversight by CC DSMC*
*** For questions regarding use of OnCore see Cancer Center Procedures or call 434-243-7064*

If this study DOES NOT require oversight by the CC DSMC (i.e. in the table above – the row you checked has a NO in the third column), DO NOT answer questions #2 and 3.

2. What is the risk level of this study?

Check One	Risk Level	Examples	Safety data Monitoring Frequency by CC DSMC	Monitoring Frequency by VPR Compliance Monitors	Additional Requirements
	High	• Investigator sponsored IND/IDE regardless of phase • Phase I trials • Gene therapy • NIH has designated as High Risk	Monthly	Every 6 months *See Table A below for adverse event reporting requirements*	• *PRC strongly recommends that you submit a protocol in CTEP format*
	Medium	• Interventional therapeutic trials not designated as high risk by NIH or PRC • Phase 2 trials • Phase 3 trials • Liver biopsies	Monthly	Every 12 months *See Table B below for adverse event reporting requirements*	• *PRC strongly recommends that you submit a protocol in CTEP format*
	Low	• Interventional non-therapeutic trials (i.e. no therapeutic intention) • Nutritional or behavioral studies • Cancer Prevention trials • Diagnostic trials • Palliative trials • Counseling trials • Skin biopsies • Blood draws	Annually via OCR QAP review.	Every 12 months *See Table C below for adverse event reporting requirements*	
	Exempt	• Non-interventional trials • Epidemiology research • Surveys / Quality of Life studies • Imaging trials • Database protocols • Tissue banking protocols	N/A	N/A – studies not monitored by the CC DSMC	

3. What are the reporting requirements for AEs of this study?

The following tables may be modified as appropriate.
The IRB recommends consultation with the CC DSMC prior to modifications.
The IRB, the PRC or the CC DSMC has the authority to overrule the monitoring frequency required as listed in the tables below.

Table A: High Risk Studies
Reporting requirements for AEs that occur within 30 days of the last dose of protocol specified treatment

	Grade 1	Grade 2		Grade 3				Grade 4 & 5
	Expected and unexpected	Expected	Unexpected	Expected		Unexpected		Expected and Unexpected
				Without hospitalization	With hospitalization	Without hospitalization	With hospitalization	
Unrelated Unlikely	OnCore 30 days	OnCore30 days	OnCore 30 days	OnCore 30 days	OnCore 15 days	OnCore 30 days	OnCore 15 days	OnCore 7 days
Possible Probable Definite	OnCore 30 days	OnCore30 days	OnCore15 days	OnCore 30 days	OnCore 15 days	OnCore 7 days	OnCore 7 days	OnCore (24-hrs)* 7 days

*Enter into OnCore database within 24 hours if unexpected and definitely related to protocol specified treatment Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours

Table B: Medium Risk Studies
Reporting requirements for AEs that occur within 30 days of the last dose of protocol specified treatment

	Grade 1	Grade 2		Grade 3				Grade 4 & 5	
	Expected and unexpected	Expected	Unexpected	Expected		Unexpected		Expected	Unexpected
				Without hospitalization	With hospitalization	Without hospitalization	With hospitalization		
Unrelated Unlikely	Not required	Not required	Not required	OnCore 30 days	OnCore 15 days	OnCore 30 days	OnCore15 days	OnCore15 days	OnCore15 days
Possible Probable Definite	OnCore30 days	OnCore30 days	OnCore15 days	OnCore30 days	OnCore15 days	OnCore 15 days	OnCore15 days	OnCore 15 days	OnCore(24-hrs)* 7 days

*Enter into OnCore database within 24 hours if unexpected and definitely related to protocol specified treatment Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours

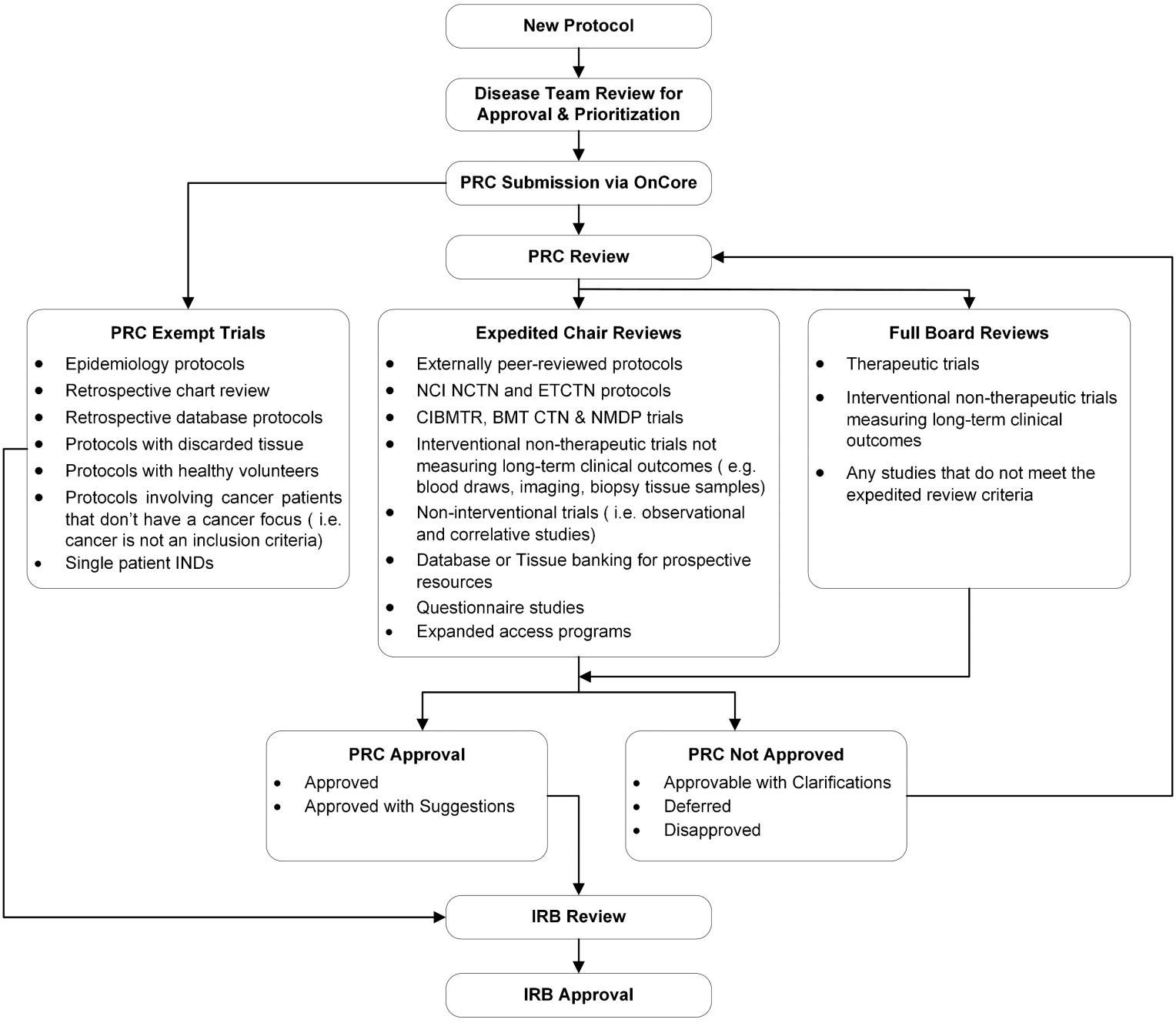
Table C: Low Risk Studies
Reporting requirements for AEs that that occur within 30 days of the last protocol specified treatment/intervention

	Grade 1-2	Grade 1-2		Grade 3	Grade 4-5
	Expected	Unexpected		Expected or Unexpected	Expected or Unexpected
		Without hospitalization	With hospitalization		
Unrelated Unlikely	Not required	Not required	Not required	Not required	OnCore 15 days
Possible Probable Definite	Not required	Not required	OnCore30 days	OnCore 15 days	OnCore (24-hrs)* 15 days

*Enter into ONCORE database within 24 hours if unexpected and definitely related to protocol specified treatment Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours

Appendix C

University of Virginia Comprehensive Cancer Center Protocol Review Process



Appendix D

Auditing by Risk Level

	Monitoring Visit	Informed Consent Review	Eligibility Review	Data Review (safety, dosing, efficacy, etc.)	Critical Document Review	Device or Drug Accountability
Risk Level	**Frequency**	**% Cases**	**% Cases**	**% Cases**	**Frequency**	**Frequency**
High	6 Months or Annual**	100	10*♦	10*♦	6 Months or Annual	6 Months or Annual
Medium	Annual	100	10*♦	10*♦	Annual	Annual
Low (therapeutic)	Annual	100	10*♦	10*♦	Annual	Annual
Low (non-therapeutic)	Annual	10*	NA	NA	NA	NA
Exempt	NA	NA	NA	NA	NA	NA

* If the specified % is < 3 cases, a minimum of 3 will be reviewed. If ≤ 3 patients have been enrolled since the last visit, all will be reviewed. If no patients are on active treatment then patients in active follow-up will be reviewed.
♦ If major deviations are noted at an audit, the DSMC or auditor may recommend an increase in frequency and % of cases for subsequent visits until a satisfactory audit is obtained.
** If High Risk trial receives 2 “satisfactory” audits within 12 month timeframe, then the frequency at which audits occur will be reduced to annual audits.
NA Not applicable.

Appendix E

Disease Teams and Chairs

Team	Chair/co-Chair
GU oncology	Robert Dreicer, MD
GI oncology	Tri Minh Le, MD; Paul Kunk, MD
Breast oncology	Patrick Dillon, MD; Christiana Brenin, MD
Head & Neck	Varinder Kaur, MD
Melanoma	Craig Slingluff, MD; Elizabeth Gaughan, MD
Thoracic oncology	Ryan Gentzler, MD; Richard Hall, MD
Gyn Oncology	Linda Duska, MD
Phase 1	Matthew Reilley, MD
Neuro-oncology	David Schiff, MD
Lymphoma/Myeloma	Craig Portell, MD
Leukemia/MDS	Firas El Chaer, MD; Michael Keng, MD
Stem Cell Transplant/ Cellular Therapies	Indu Varadarajan, MD; Karen Ballen, MD
Pediatric oncology	Brian Belyea, MD