



University of Virginia Cancer Center

Data and Safety Monitoring Plan for Clinical Research

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1. Introduction

The University of Virginia Cancer Center (UVaCC) has responsibility for overseeing the conduct of cancer-related clinical trials that involve research activities related to cancer. The University of Virginia 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, 1999 (<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 Cooperative Group Data Monitoring Committee Policy (Phase 3 Trials) can be found at <http://ctep.info.nih.gov/monitoring/index.html>. 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/clinicaltrials/patientsafety/dsm-guidelines>.

In accordance with the NIH requirements, the UVaCC has developed an Institutional Data and Safety Monitoring Plan that outlines appropriate oversight and monitoring of all cancer-related interventional studies. The purpose of the data and safety monitoring plan 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 UVaCC 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 IRB, the PRC, the DSMC, the Office of the Vice President for Research (VPR) Post Approval Monitoring (PAM), and the Cancer Center's Clinical Trial Advancement Committee (CTAC).

Institutional Review Boards are managed by the Office of the VPR to insure 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 UVaCC, the Protocol Review Committee (PRC) and the Data and Safety Monitoring Committee (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 a 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 scientific 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 PAM branch of the Office of the VPR 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 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 vast majority of research protocols involving cancer patients fall under the domain of the IRB-HSR.

A small number of protocols will be 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-SBC. These studies receive oversight by the PRC but are not monitored or audited by the DSMC or the Office of the Vice President for Research Post Approval Monitoring and Education Program (PAM and ED).

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, risk-to-benefit ratio; and where applicable, monitoring frequency. NCI cooperative group trials will not be assigned a risk level, risk-to-benefit ratio or an oversight responsibility; as they are exempt from scientific review (please see section 2.2 for more information on PRC exemptions). The PRC Chair and PRC Coordinator receive IRB agendas and minutes in order to ensure that no protocol is submitted for IRB review without the appropriate PRC review (The IRB also receives PRC meeting minutes. The IRB can occasionally request that the PRC review

NCI-cooperative-group studies because of IRB concerns about possible unfavorable risk/benefit ratios or scientific merit).

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: <http://www.medicine.virginia.edu/administration/office-of-the-dean/administration/school-policies/Conflictsofinterest.pdf>

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) (<http://leg1.state.va.us/cgi-bin/legp504.exe?000+cod+TOC0202000003100000000000>) and the Governor's Executive Order 16 (2006) ([http://www.lva.virginia.gov/public/EO/eo16\(2006\).pdf](http://www.lva.virginia.gov/public/EO/eo16(2006).pdf)).

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;
- c) closely monitoring the accrual progress of studies in the Cancer Center.

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:

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

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.state.va.us/hrpolicy/web/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 (<http://www.medicine.virginia.edu/administration/office-of-the-dean/administration/school-policies/ConflictsOfInterest.pdf>). 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 review from the full Committee.
- b. **Non-therapeutic interventional trials** (i.e. prevention, supportive care, screening, early detection, diagnostic studies) usually require review from the full committee, 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.

2. **Non-interventional protocols** (i.e. epidemiologic, observational, correlative studies) are reviewed solely by the Chair of the PRC or his designee

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 in the OnCore database. They are reviewed for competition monthly.

3. Trials Exempt from PRC review:

- Database protocols (protocols to establish or renew a database).
- Retrospective chart review . True epidemiology protocols
- Protocol that study discarded tissue and correlate with chart review
- Protocols involving cancer patients that do not have a cancer focus.

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

PIs submit therapeutic and interventional non-therapeutic protocols to the PRC. These studies receive review by the full Committee, consisting of at least two medical reviews, one biostatistician review, data and safety monitoring plan (DSMP) review and CRC review. If the protocol utilizes an investigational agent, a review is obtained from the clinical pharmacist. The PRC seeks review from *ad hoc* reviewers when needed if the Committee members are not qualified to adequately review the proposed study.

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

- Study Protocol IRB-HSR Application (if applicable)
- Investigator Drug Brochure (if applicable)
- Investigator Device Brochure (if applicable)
- Study Related Documents

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

1. Scientific merit, with an emphasis on the following:
 - Design and management of protocol
 - Relevance and completeness of background information
 - Clarity and appropriateness of eligibility criteria
 - Consistency of outcome with study objectives
 - Feasibility of achieving study objectives, and suitability of methods (including appropriate blinding/masking procedure and/or appropriate randomization)
 - Implications of the study (i.e. increased survival, remissions, and decreased toxicity)
 - Appropriateness of intended accrual period
 - 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 premedications
- 3. Biostatistical analysis
 - Inclusion of stopping rules and interim analyses
 - Appropriateness of sample size and statistical analysis method
- 4. CRC criteria
 - Eligibility criteria
 - Data management
 - Resource availability
- 5. Data and Safety Monitoring Plan
 - Completeness of Data Safety Monitoring Plan
 - Ensuring the protocol and DSMP correlate

Based on the review, the Committee issues one of four findings on both the protocol and DSMP:

1. Approved as written;
2. Contingent approval (minor clarifications or revisions required; submitted revisions may be approved by Chair or his designee);
3. Deferred (major revisions or clarification required; protocol must be re-submitted to full Committee review);
4. Rejected. (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. If the PI 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 approval can be given, PIs' revisions and responses must address all issues raised by the previous review. If reviewers required a mandatory revision(s), PIs must submit an updated protocol or DSMP with tracked changes. 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. The PRC Coordinator notifies the PI and the IRB when approval is granted, and issues an approval form.

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
- IRB-HSR Application (if applicable)

- Study Related documents

These trials are eligible for PRC review by the Chair only or his designee, using the same criteria as is used for full Committee reviews. Trials appropriate for review by the Chair only may be submitted and reviewed independently of the monthly deadline for full Committee review. Protocol reviews by the Chair only or his designee are completed within 14 days, a timeline which is comparable to that for full Committee 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. investigator-initiated trials;
2. non-UVA investigator-initiated trials;
3. cooperative group protocols;
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

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 accrual opens and ends when accrual is closed. Accrual is reviewed 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.

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 of concern 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
- Yearly 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 response from study team is satisfactory PRC may reopen study to accrual.

Accrual data is entered monthly into OnCore. Using this information, the PRC Coordinator provides reports on non-accruing trials that meet performance review criteria for review by the PRC in May and November. 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 managing office 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; and b) the PI can request to add investigators on a trial. 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. If a study was reviewed for non-accrual or slow accrual at the previous review, the study may 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 and a risk-to-benefit ratio as requested by the IRB-HSR 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)
- DSMC oversight not required (): non-interventional trials (epidemiology research, survey, imaging or functional assessment).

The risk-to-benefit ratio allocation as requested by the IRB-HSR for each study is as follows:

- 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

The PRC reviews revisions of all 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 investigator-initiated cancer-related therapeutic or non-therapeutic intervention trials.

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, the IRB-HSR application and the most current version of the informed consent documents. DSMC summary reports are submitted to the committee members approximately one 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 full DSMC committee meeting.

2.3.1 DSMC Membership

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

2.3.2 Confidentiality Procedures

No communication, either written or verbal, of the deliberations or recommendations of the DSMC will be made outside of the DSMC except as provided for in this policy. If issues are

identified at the meetings, DSMC deliberation/recommendations will be discussed with PRC, IRB, Cancer Center senior leadership in the CTAC, and the Office of the Vice President of Research. 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.state.va.us/hrpolicy/web/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 UVaCC official(s), in accordance with in accordance with the UVa SOM Policy on Conflict of Interest and Conflict of Commitment (<http://www.medicine.virginia.edu/administration/office-of-the-dean/administration/school-policies/Conflictsofinterest.pdf>). 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 monthly, on the third Monday of the month, which is one week prior to the PRC meeting on the fourth Monday of the month. During the week prior to the DSMC meeting, the PRC/DSMC Coordinator sends updated information about protocols that require review to all members via e-mail.

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, at least two physicians and two non-physicians must be present at the meeting.

2.3.5 DSMC Responsibilities

At the meetings, DSMC members will 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, PAM 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. Semiannual data audits are required for all High-risk studies and annual data audits required for Medium- and Low-risk studies. Monitoring by the DSMC ends 30 days after the last active patient completes protocol treatment unless additional monitoring is deemed necessary by the Committee, PI, or IRB-HSR.

A determination of the degree of monitoring by the UVa CC 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 trial will require a DSMP and monitoring by the DSMC or an external DSMB.
- *Multi-institutional UVa investigator-initiated*: any high/medium risk phase III multi-institutional, UVa investigator-initiated trial will require a DSMP and monitoring by an external DSMB. Any high/medium risk pilot, phase I or phase II; or low risk phase III multi-institutional UVa investigator-initiated trials will require a DSMP and monitoring by the DSMC. Depending upon the complexity of the trial and the target accrual, the DSMC may request that an external DSMB monitor the study.
- *Multi-institutional non-UVa investigator-initiated*: any multi-institutional trial conceived and initiated by another institution with subsequent UVa CC

participation will require DSMPs that have been reviewed and approved by the PRC and IRB. DSMC monitoring will not be required.

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 Post Approval Monitoring (PAM)

In pursuit of the University of Virginia's commitment to the protection of human subjects involved in research and to satisfy federal regulatory agencies, a Human Subject Research Post Approval Monitoring (PAM) Program is conducted within the Office of the Vice President for Research (VPR). The purpose of the program is to assess clinical research activities conducted under the University's Federal Wide Assurance Agreement with the Office of Human Research Protections, providing internal oversight on compliance issues related to the performance of human research trials.

There are four program objectives:

- 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 ensure compliance with federal, state, local and institutional regulations and guidelines
- To identify areas of strength and areas needing improvement in research policies and practice

This program is utilized to conduct compliance audits for the Cancer Center DSMC. The extent of auditing is determined by the risk and the sponsor of the study. Standard

Operating Procedures (SOPs) for the Post Approval Monitoring Program (PAM) can be found at www.virginia.edu/vpr/pam.

Any study under the purview of the University of Virginia HSR-IRB or HSR-SBS is subject to review. Studies are chosen either a) at random or b) requested by a study team member or any member of the IRB-HSR and the DSMC.

2.4.1 Procedures for internal audits (PAM audits)

The audit procedure is a formal, broad, source document review of any 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. A study will be triggered for an audit once 3 patients have been registered in OnCore.

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. If findings are satisfactory after two reviews, protocols will be audited once a year. Any time findings are unsatisfactory, auditing will return to the original schedule.

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 PAM 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 PAM Working Group, the PAM IRB-HSR Advisory Committee and the DSMC. Through this process, these committees provide for quality assurance activities for cancer-related studies.

2.5 OCR Compliance Audits

The Education and Compliance division of the Office of Clinical Research (OCR) has been established to facilitate and implement an “audit ready” environment for all UVa CC clinical trials using non-punitive audits/reviews in combination with education. The OCR’s intention is to complement the efforts of the PAM monitoring group. An OCR audit of a CC clinical trial would be initiated for the following indications but not limited to the following:

1. Change of Clinical Research Coordinator
2. Workload and FTEs are unbalanced due to change in staff
 - a. Number of open protocols, active patients, accrual vs. amount of staff
3. Orientee’s will receive an audit 6 months from hire date
4. The OCR Compliance and Education Specialist 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
5. At the request of the PAM Group
 6. At the request of a study team member

2.6 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
- 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 UVaCC 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 UVaCC investigator-initiated clinical trial, the PI must clearly identify the UVaCC as the coordinating center in the protocol and define the responsibilities of all affiliate centers. PIs sponsoring multi-center UVaCC 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 UVaCC investigator-initiated trials are expected to comply with this DSMP. As such, all sites will use the UVaCC-created CRFs/eCRFs designed for the study. All data are entered into OnCore. 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 PAM 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 UVaCC 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 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 Harmonisation (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.

3.1.4 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 becomes obvious. These IRB-HSR decisions are likewise subject to appeal. However, decisions regarding protocol termination cannot be appealed to the PAM committee.

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.

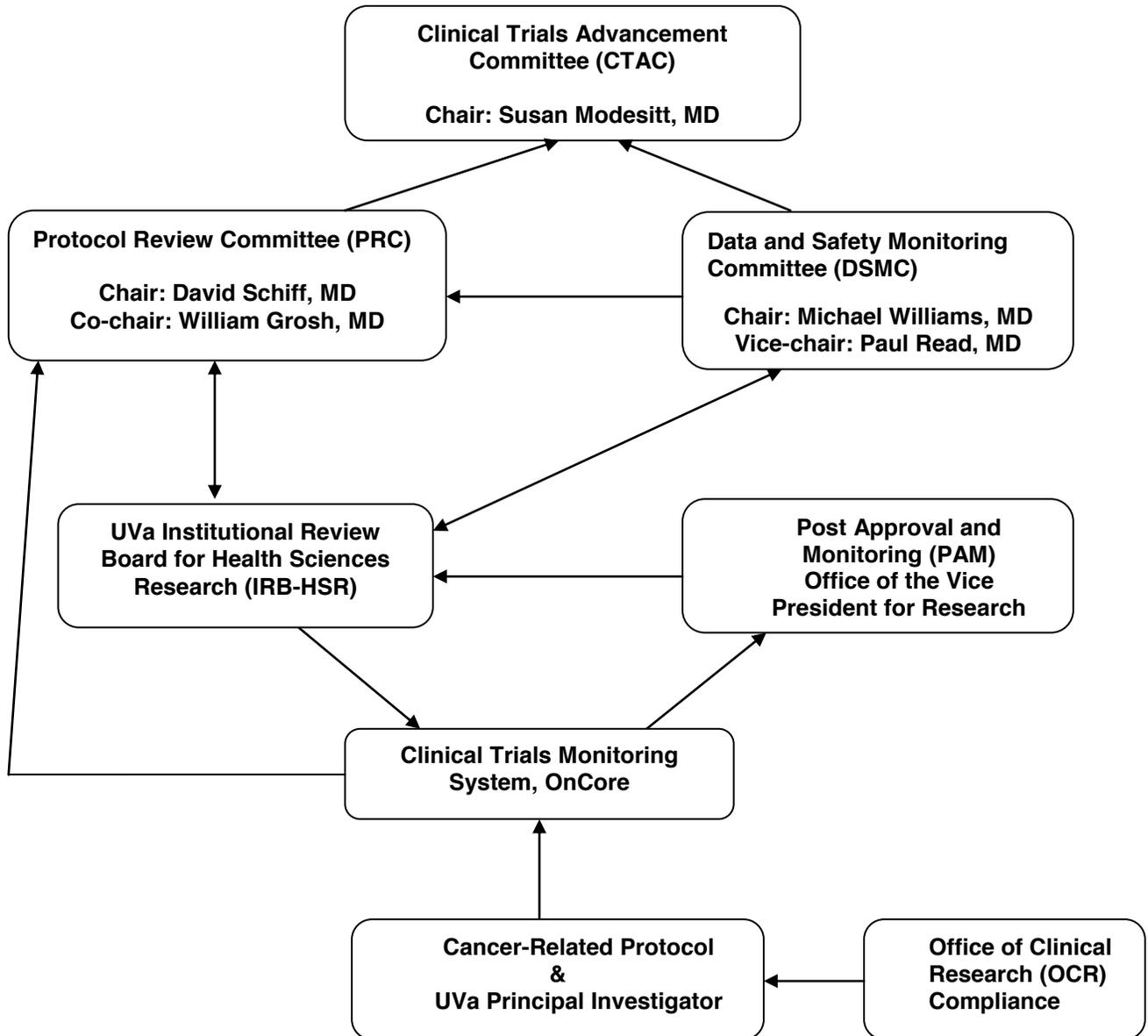
When any of the monitoring bodies suspends enrollment or closes a study for whatever reason, the study team is responsible for notification of all investigators involved with the study at UVaCC and any external sites, the IRB, the sponsor and any funding agency as applicable. Written documentation of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

5. Summary

UVaCC 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 UVaCC 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 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	<i>If determined by NIH or IRB</i>	<i>Enrollment/ accrual information must be submitted to OnCore. **</i>
	Industry sponsored	No	<i>If determined by sponsor or IRB</i>	<i>• Enrollment/ accrual information must be submitted to OnCore **</i>
	UVa Investigator Initiated- Single site at UVa	Yes*	<i>If determined by PRC, NIH or IRB</i>	<i>• Enrollment/ accrual information must be submitted to OnCore **</i>
	UVa Investigator Initiated (Multi-site)	Yes*	<i>Yes if: Phase III- Medium or High Risk; or determined by PRC, NIH or IRB</i>	<i>• Enrollment/ accrual information must be submitted to OnCore **</i>
	Non- UVa Investigator Initiated (Multi-site)	No	<i>IRB to determine</i>	<i>• Enrollment/ accrual information must be submitted to OnCore **</i>

**Oversight required by either CC DSMC or an External Board. To be determined by Cancer Center PRC.
** For questions regarding use of OnCore see [Cancer Center Procedures](#) or call 434-243-7064
The IRB, the PRC or the CC DSMC has the authority to overrule the oversight required as listed in the table above.*

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	Monitoring Frequency by VPR Compliance Monitors	Additional Requirements
	High	<ul style="list-style-type: none"> Investigator sponsored IND/IDE regardless of phase Phase I trials Gene therapy NIH has designated as High Risk 	Every 6 months <i>See Table A below for adverse event reporting requirements</i>	<ul style="list-style-type: none"> PRC strongly recommends that you submit a protocol in CTEP format
	Medium	<ul style="list-style-type: none"> Interventional therapeutic trials not designated as high risk by NIH or PRC Phase 2 trials Phase 3 trials Liver biopsies 	Every 12 months <i>See Table B below for adverse event reporting requirements</i>	<ul style="list-style-type: none"> PRC strongly recommends that you submit a protocol in CTEP format
	Low	<ul style="list-style-type: none"> 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 	Every 12 months <i>See Table C below for adverse event reporting requirements</i>	
	PRC review not required	<ul style="list-style-type: none"> Non-interventional trials Epidemiology research Surveys / Quality of Life studies Imaging trials Database protocols 	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	OnCoreRE 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

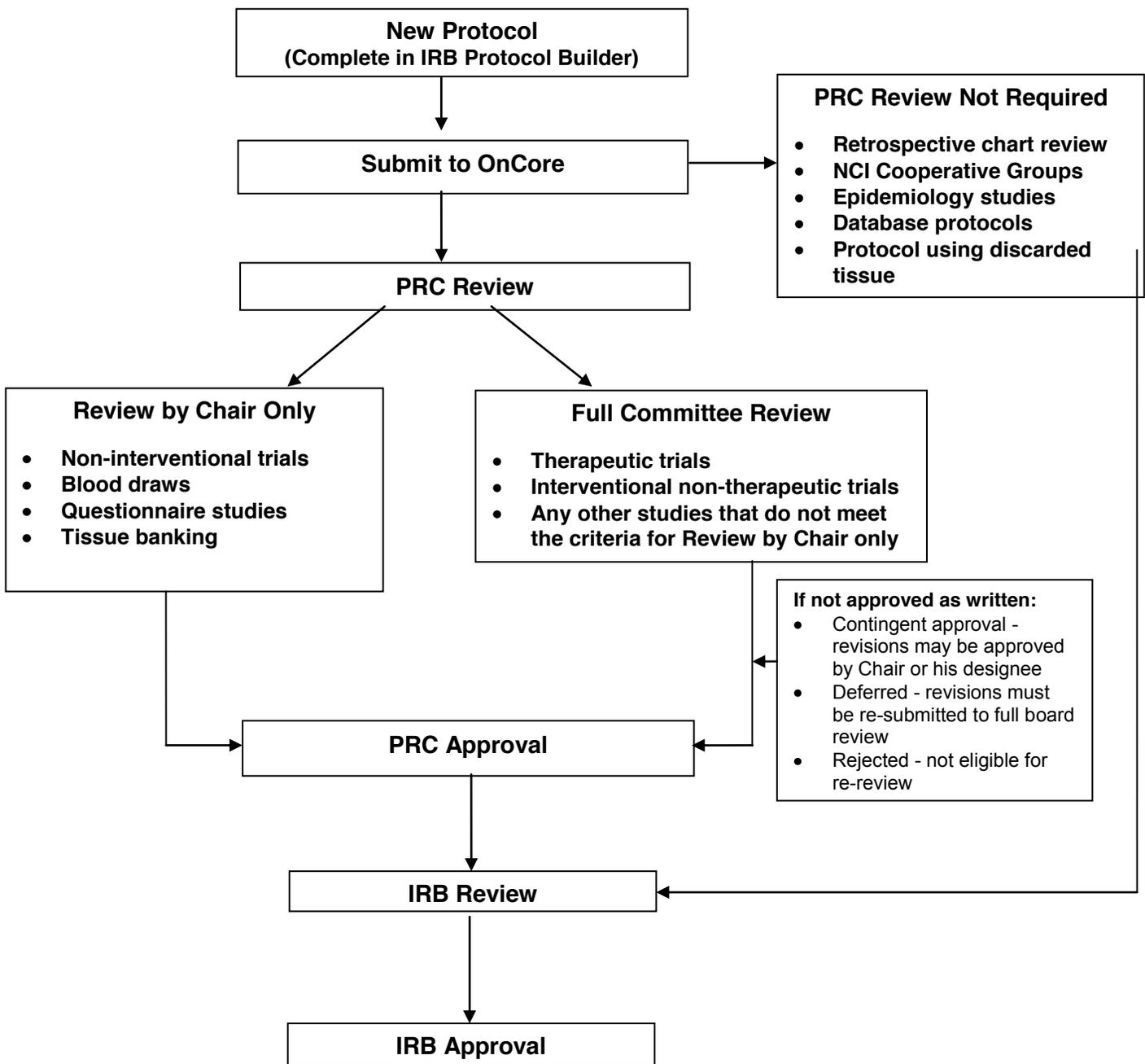
*Enter into OnCore database within 24 hours if unexpected and definitely related to protocol specified treatment
Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours

Table C: Low Risk Studies						
Reporting requirements for AEs that occur within 30 days of the last protocol specified treatment/intervention						
	Grade 1-2		Grade 1-2		Grade 3	Grade 4-5
	Expected	Unexpected	Unexpected		Expected or Unexpected	Expected or Unexpected
			Without hospitalization	With hospitalization		
Unrelated Unlikely	Not required	Not required	Not required	Not required	Not required	OnCore 15 days
Possible Probable Definite	Not required	Not required	OnCore30 days	OnCore 15 days	OnCore 15 days	OnCore (24-hrs)* 15 days

*Enter into ONCOREONCORE 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 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.