CANCER CONSORTIUM

FRED HUTCH • UNIVERSITY OF WASHINGTON • SEATTLE CHILDREN'S

INSTITUTIONAL DATA AND SAFETY MONITORING PLAN

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Responsible Office: Office of the Director

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Introduction

This Data and Safety Monitoring Plan (DSMP) covers human subjects research conducted under the auspices of the Fred Hutch/University of Washington/Seattle Children's Cancer Consortium (hereafter referred to as the Consortium), comprising three academic partners: Fred Hutchinson Cancer Center, the University of Washington (UW), and Seattle Children's (SC).

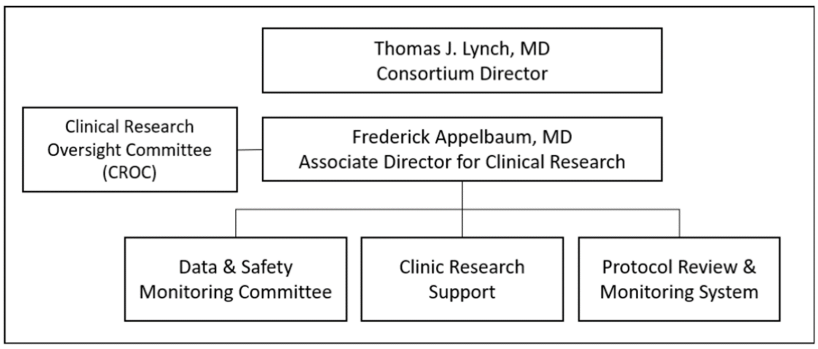
The Consortium places the highest priority on ensuring the safety of human subjects participating in research studies. The Cancer Center Director, the Associate Director for Clinical Research, the Medical Director of Clinical Research Support (CRS), and the CRS Administrative Director hold ultimate responsibility for the oversight and execution of the DSMP. The Consortium is fully committed to ongoing review and refinement of its processes and oversight mechanisms to assure subject safety, data validity and integrity, and regulatory compliance.

The broad scope of this plan includes all cancer and cancer-related, prospective human subjects research conducted by Consortium members or enrolling subjects at the Consortium institutions. The plan is developed to account for the needs of investigator-initiated trials funded institutionally or through NIH or other peer-reviewed funding, and for trials sponsored and monitored by external organizations, with particular focus on quality control and assurance of institutionally sponsored, investigator-initiated research, and those trials without external oversight. This DSMP does not take the place of IRB policies, Food and Drug Administration (FDA) requirements, or special National Institutes of Health (NIH) guidelines, such as the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*.

Overview

All Consortium clinical research is governed by the oversight structure outlined in Figure 1. The Clinical Research Oversight Committee (CROC) assists the Associate Director for Clinical Research (AD CR) to set the vision and standards for how clinical research is conducted across the Consortium and ensures adherence with all regulations and sets and enforces Consortium policies. Consortium DSM is required for all prospective human subjects research. The DSM has three components: 1) the Consortium's NCI-approved Data and Safety Monitoring Plan (DSMP), 2) the Data and Safety Monitoring Committee (DSMC) and its Compliance Sub-Committee, and 3) the CRS Quality Assurance and Education Unit. The Consortium PRMS is a two-stage review mechanism that is responsible for approving, prioritizing, and monitoring scientific progress of interventional clinical trials.

Figure 1. Consortium Clinical Research Oversight Structure



Clinical Research Oversight Committee (CROC)

The CROC ensures that all aspects of the clinical research process are conducted according to Consortium policies, procedures, and best practices. The DSMC may escalate to CROC any compliance issues brought forward by the DSMC Compliance Sub-Committee, and CROC is the highest level of governance responsible for enforcing remediation activities for faculty, staff, or entire programs.

The CROC has the following functions:

- Sets and enforces all Consortium policies and procedures related to clinical research.
- Oversees all cancer clinical trials conducted in the Consortium.
- Advises the Cancer Center Director on appointments to the Scientific Review Committee (SRC) and the Data and Safety Monitoring Committee (DSMC).

The CROC does not review SRC decisions, nor does it review clinical trials for scientific merit or accrual. CROC does not in any way overlap, override, or interfere with the authority of DSMC or SRC.

The CROC is chaired by the AD CR and includes clinical research leaders and faculty representatives from all three Consortium institutions. The Cancer Center Director appoints Consortium Leaders to serve on the CROC for a 3-year term that is renewable with consent from the Director. In general, the committee meets quarterly. Additional meetings are scheduled as necessary to address specific issues that affect subject safety.

Clinical Research Support (CRS)

Clinical Research Support (CRS) serves as the Consortium's central clinical trials office and enables integrated review, approval, activation, and conduct of all cancer clinical trials in accordance with Consortium DSMP. It supports investigators in the conduct of high quality, compliant clinical research through active administrative support of PRMS, DSM, and other clinical research committees; comprehensive education and training; centralized protocol development and implementation; day-to-day study coordination; IND submissions and management; standardized procedures and templates; clinical research information systems; and unified data collection and reporting (Appendix A).

The CRS Quality Assurance and Education Unit performs ongoing monitoring and auditing to ensure protocol compliance with all Consortium policies and procedures, IRB policies, FDA regulations, ICH-GCP, and the DSMP, as well as adherence to the protocol. Every Consortium interventional clinical research protocol is required to include a protocol-specific DSM plan that meets the requirements outlined in this document and must be approved by the CRS Quality Assurance team.

Protocol Review and Monitoring System (PRMS)

A single Protocol Review and Monitoring System (PRMS) governs all oncology clinical research across the Consortium partner institutions. The Consortium PRMS is a two-stage review mechanism that is

responsible for approving, prioritizing, and monitoring scientific progress of interventional clinical trials. All trials are included - industry-sponsored, NCTN, NIH, unfunded - regardless of funding source.

Cancer-related trials are those:

- Funded by NCI; or
- Primary site of a multi-site trial has classified the study as cancer or cancer-related; or
- The trial cohort will include both patients with a cancer diagnosis and others without a cancer diagnosis AND includes a primary or secondary analysis of the portion of the cohort with a cancer diagnosis; or
- Research of secondary conditions related to cancer treatment in patients with a cancer diagnosis who have received that treatment; or
- Cancer prevention studies that specifically include a primary outcome of cancer diagnosis.

An interventional trial is research in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Research Group Review

The first stage review, Research Group Review, is conducted by one or more of the established Consortium Research Groups.

Structure and Membership

The first stage Research Group review is comprised of investigators organized according to 16 specific disease sites and modalities with ongoing clinical trials and each group has an appointed Director. A list of Research Groups and Research Group leadership can be found in the Appendix C: Committee Rosters.

Review Criteria and Process

Research Groups are responsible for the initial assessment and prioritization of concepts and protocols for scientific merit, feasibility, fit with the patient population and needs of the catchment area, and potential to recruit and retain women, minorities, special populations, and individuals across the lifespan as appropriate for the scientific goals of the research.

New trials must have documented approval by the appropriate primary Research Group and secondary Research Group if applicable, prior to submission to the Scientific Review Committee. If a concept or clinical trial involves more than one disease or modality, collaboration with other Research Groups is documented during the review.

The Research Group Review informs the SRC on how competing trials will be managed within the Research Group program's portfolio. Documentation of the review must include an operational priority score that determines which protocols may be submitted for SRC review and ensures prioritization of research efforts and resource allocation. The Research Group may determine a trial is not feasible if there are substantive issues and disapprove moving forward to SRC.

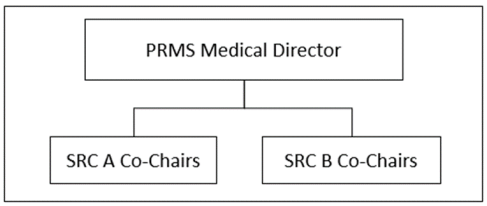
Scientific Review Committee

The second stage review is performed by the Consortium Scientific Review Committee (SRC).

Structure and Membership

The SRC is comprised of two multi-disciplinary subcommittees, SRC A and B, each led by a Chair and Co-Chair who report to the PRMS Medical Director (Figure 2). Both subcommittees adhere to the same process, scope for review, and membership composition. Membership on both sub-committees is representative of all major clinical research areas of the Consortium. SRC Membership can be found in the Appendix C: Committee Rosters. Committee members are appointed by the AD CR for a three-year term; appointment is renewable.

Figure 2. SRC Structure



Review Criteria and Process

Once a protocol receives endorsement and an overall priority score from the relevant Research Group(s), it can proceed to SRC submission and review. SRC review consists of a scientific and statistical review. Its responsibilities do not overlap with the IRB, which focuses on ethical and regulatory review requirements; or with the DSMC, which provides data and safety monitoring functions.

New protocols are reviewed for the following: scientific merit, study design (including biostatistics), feasibility of achieving accrual goal including consideration of competing trials, alignment with catchment area needs and Consortium strategic priorities, and the trial's potential to include women, minorities, special populations, and individuals across the lifespan as appropriate for the scientific goals of the research. A protocol may require an expedited or full review.

> Expedited Review: New protocols that may have an expedited SRC review include NCTN trials, extension trials, and multicenter trials that have been reviewed by the PRMS of another Cancer Center with an NCI fully approved PRMS (See Multicenter PRMS Reliance). Expedited reviews are conducted solely by the SRC Chair and consider the same documents reviewed by the full SRC. PRMS approval documentation is required for the expedited review of multicenter trials that have been approved by another Cancer Center's NCI fully approved PRMS, per multicenter PRMS Reliance.
>
> Full Review: New protocols that do not meet the SRC criteria for expedited review receive full review. Each protocol is assigned two reviewers and a biostatistician. Full committee review requires a quorum which is met with the presence of at least eight core SRC members, including a biostatistician, and results in committee vote.

Review Outcomes

Committee review results in one of three review outcomes:

1) Full approval (with no further action required),
2) Conditional approval (changes required), or
3) Disapproved.

Written documentation of the meeting outcome is provided to the PI in the form of a result letter. PI response to a conditional approval (non-approval because minor changes or responses are required) may

be reviewed and approved by the original reviewers and the Chair. Resubmissions after disapproval because of major changes must be re-reviewed by full committee.

A new protocol must receive full approval by the SRC, including approval of SRC required changes, before it can proceed to the IRB.

Multicenter PRMS Reliance

PRMS approval documentation is required for the expedited review of multi-site trials that have been approved by another Cancer Center's NCI fully approved PRMS, per Multi-site PRMS Reliance. For multi-site trials, the Consortium SRC may perform an expedited review as it may rely on the lead site's full committee review. In such cases, all criteria must be met: 1) The site has and provides an assertation of an NCI fully approved PRMS, 2) the site is an NCI-designated Cancer Center, and 3) review documentation proves full PRMS approval of the new protocol.

Monitoring for Scientific Relevance

To ensure scientific merit throughout the life of the clinical trial, scientific reviews are conducted for applicable protocol amendments. Institutional and Externally Peer-Reviewed trials may require full SRC review for amendments that significantly alter the research design, the scope of the investigation, or the scientific basis or objectives of the trial.

The SRC does not review protocol amendments for trials sponsored by industry or NCTN trials as these changes have been thoroughly reviewed for scientific merit outside of the Consortium. In addition, the SRC does not review amendments for trials which are permanently closed to accrual locally.

Accrual Monitoring

The SRC monitors accrual of all active trials to assess scientific progress and diversity. Accrual is reviewed annually to determine progress in achieving its targeted accrual rate and enrollment of women, minorities, and individuals across the lifespan from the catchment area. The SRC has the authority to close any trial that does not meet accrual requirements as defined by the Consortium's Low Accrual Policy. PIs and Research Group Directors can appeal closure to the SRC, however, only one closure appeal is allowed per trial. For those trials not meeting targeted accrual diversity, the PI is referred to the Office of Community Outreach and Engagement recruitment and retention resources.

PRMS Conflict of Interest

Financial and non-financial conflicts of interest are managed throughout the PRMS review processes and ensure that:

- Research Group Directors or designees do not serve as signatory for the approval of new protocols in which a financial or non-financial conflict exist.
- SRC members do not participate in the review or voting process for trials in which a financial or non-financial conflict exist for Covered Persons.

Covered Persons within the PRMS are SRC members, Chairs, Co-Chairs, and Research Group Directors or designees. All Covered Persons with potential financial or non-financial conflict of interest related to a trial, are recused from review to prevent such conflicts from interfering with the objectivity and validity of the review process.

Research Group Non-Financial Conflict is defined as the following:

- The Principal Investigator of the protocol under review by the Research Group(s)

SRC Non-Financial Conflict is defined as any of the following:

- Principal Investigator of the protocol under review by the SRC;
- Biostatistician involved in design of the protocol under review by the SRC; or
- Research Group Director or designee responsible for approving submission of an assigned protocol for review by the SRC and signing the Research Group Review Summary Form.

Data and Safety Monitoring Committee (DSMC)

Oversight by the Consortium's DSMC and Compliance Sub-Committee ensure protocol compliance, data quality, and patient safety. The DSMC is responsible for reviewing all Consortium investigator-initiated trials to assure a trial is conducted in compliance with the protocol, institutional policies, and regulations, and that participants safety, rights, and welfare are protected.

Structure and Membership

The DSMC is led by a committee chair and membership is representative of the primary clinical research areas of the Consortium. Members are appointed by the AD CR for a three-year term and is renewable as determined by the AD CR. The DSMC functions independently of the SRC and there is no overlap in roles or committee composition. DMSC Membership can be found in Appendix C: Committee Rosters.

Scope and Process:

All interventional trials with a drug, device, or biologic and have enrolled at least one participant, are subject to annual DSMC review. DSMC is not required for trials that are permanently closed to accrual with no enrollments or participants having received study treatment in the previous year.

The scope of DSMC review differs depending on whether a trial has a dedicated DSMB.
For trials without a DSMB, the DSMC will review:

- Number of subjects,
- Unanticipated problems,
- List of Stopping Rules met, if applicable,
- List of dose-limiting toxicities and responses that have occurred in the specified timeframe,
- Premature terminations of investigational treatment and other safety issues,
- Cumulative tabulation of adverse events by type and grade, including deaths,
- All audit reports and any Major or Moderate monitoring findings,
- Compliance Summary Report (CSR) that includes compliance data from monitoring, auditing, and noncompliance reports.

For trials with a DSMB, the DSMC will review:

- Number of subjects,
- Unanticipated problems,
- Cumulative table of adverse events by type and grade, including deaths,
- DSMB minutes and reports for accrual, stopping rules, adherence to protocol DSMP; and

DSMB recommendations,
- All audit reports and any Major or Moderate monitoring findings,
- Compliance Summary Report (CSR) that includes compliance data from monitoring, auditing, and noncompliance reports.

The DSMC does not review trials that are monitored by an external entity, including national cooperative group trials and industry-sponsored clinical trials.

DSMC Outcomes:
The DSMC assigns an outcome of full approval, conditional approval, or suspension as defined below.
- Full Approval: Accrual may continue, no changes required; if closed to accrual, no changes required.
- Conditional Approval: Accrual may continue, but additional clarification regarding data submitted may be required.
- Suspension: Accrual must stop until all necessary protocol changes are made, investigational treatment may continue for previously enrolled subjects (determined on a trial-by-trial basis).

DSMC has the authority to temporarily suspend or permanently close a trial to further enrollment due to safety and/or compliance concerns. The outcome is communicated promptly to the PI and then reported, if appropriate, to the IRB.

Compliance Sub-Committee
The primary responsibilities of the DSMC's Compliance Sub-Committee are to 1) review and assess all internal and external monitoring and audit reports, 2) direct and ensure completion of Corrective and Preventive Action Plans (CAPAs), and 3) identify and assess compliance trends across the Consortium and specific to a trial, research program, or investigator.

Structure and Membership:
The sub-committee is composed of the CRS Medical Director, the CRS Administrative Director, the Director of Quality Assurance and Education, and the CRS Compliance Manager and meets monthly with ad hoc meetings convened as needed.

Scope and Process:
The sub-committee reviews compliance data for all Consortium trials. The CRS Compliance Team reviews and analyzes all internal and external monitoring and audit reports and provides the sub-committee a detailed summary and outcome for each audit report and each individual monitoring finding documented during a monitoring visit. Any monitoring finding deemed Major is reviewed in detail by the sub-committee. The Compliance Team recommends Corrective and Preventive Action (CAPA plans) for endorsement by the sub-committee and the sub-committee ensures all CAPA plans are completed according to the plan. The sub-committee also reviews compliance data for trends across programs and the entire Consortium to inform targeted quality control and assurance measures and system improvements.

Compliance Sub-Committee Outcomes:
The sub-committee has the authority to require a CAPA as part of an audit report or monitoring visit. The committee may require staff or faculty retraining, request an audit, or additional monitoring. A

Compliance Summary Report (CSR) is provided to the DSMC that includes a summary of all internal and external monitoring findings and recommendations from the Compliance Sub-Committee. Any compliance finding that may impact patient safety is reported directly to the DSMC. The sub-committee does not have the authority to suspend a trial but may recommend trial or program suspension to the DSMC or CROC (Appendix B).

Protocol Data and Safety Monitoring Plans (DSMPs)

Protocols must incorporate in their design a DSMP appropriate for the trial size, type, and risk level. CRS Quality Assurance reviews Investigational New Drug (IND)/Investigational Device Exemption (IDE) requirements and the monitoring plan to ensure consistency with the Consortium DSMP. An approved DSMP is required prior to SRC submission.

In addition, CRS conducts a prospective review of all monitoring plans for external performance sites for IITs and the protocol regulatory file is monitored for compliance with the approved plan during the conduct of the trial.

Data and safety monitoring plan requirements are outlined below:

All Trials:
For all trials, investigators conduct continuous review of data and subject safety. This ongoing review will include the number of subjects, assessment of adverse events, application of dose adjustments and/or stopping rules based on toxicities, appropriate management of dose escalation/de-escalation cohorts (if applicable), and responses observed. The trial PI will also have responsibility for establishing and carrying out procedures for assessing protocol compliance, data accuracy and completeness, and full and timely reporting of safety data. The trial PI may delegate some or all of these responsibilities to appropriately trained staff, but the trial PI maintains ultimate responsibility.

Multicenter Trials:
A plan for trial-wide data and safety monitoring must be incorporated into the protocol when one of the Consortium institutions serves as the coordinating center for multicenter trials. The overall trial PI must document that each external performance site is qualified to conduct the trial and conforms to all relevant regulations and guidelines.

Written agreements will be obtained from all external performance sites acknowledging their responsibilities for data and adverse event reporting and agreement to provide records, files, case report forms or any other documents needed to verify compliance.

The trial PI must obtain copies of all local IRB approvals and will have the responsibility for receiving the information required for adverse event reporting and safety monitoring from outside sites and disseminating that information to the appropriate Consortium committees and, when required by the protocol, a DSMB.

IND/IDE Trials:
Studies conducted under an investigational new drug application (IND) or investigational device exemption (IDE) are subject to requirements described in U.S. Food and Drug Administration (FDA) regulations under 21 CFR Part 312 (IND) or 21 CFR Part 812 (IDE). For multicenter studies conducted under an internally sponsored IND/IDE, the responsibilities described above for selection and oversight of outside study sites are specifically associated with the Sponsor obligations associated with an IND/IDE. Internal Sponsors are required to document qualifications of external performance sites and to conduct monitoring no less often than described in the protocol monitoring plan.

Phase 1 Trials:
Phase 1 trials must clearly define dose limiting toxicities, rules for escalation of dose, and criteria for stopping the trial and defining the Maximum Tolerated Dose.

A trial-specific DSMB may be required for investigator-initiated Phase 1 trials involving multiple institutions, unusually high-risk interventions (such as gene therapy or cellular immunotherapy), or unusually vulnerable populations.

Phase 2 and 3 Trials:
Phase 2 trials, where appropriate, will incorporate stopping rules for prospectively defined adverse events. The stopping rules must clearly define the events in question, the frequency with which the stopping rule will be assessed, and the threshold for stopping or modifying the trial.

For investigator-initiated Phase 3 and large Phase 2 trials, particularly those that are blinded or multicenter, a study-specific Data and Safety Monitoring Board (DSMB) will be required to review safety and other data at pre-specified intervals, at least annually.

Data and Safety Monitoring Boards (DSMBs)

A dedicated DSMB is required for all investigator-initiated Phase 3 and large Phase 2 trials. For Phase 1 or smaller Phase 2 trials, a DSMB may be appropriate if studies are multicenter, blinded, include vulnerable populations, or involve high-risk interventions (such as gene therapy or cellular immunotherapy). A DSMB is required for a trial that meets more than one of these criteria.

Prior to SRC review, the CRS Quality Assurance team reviews all protocol DSM plans to ensure Consortium DSM requirements are met, including a study specific DSMB when applicable.

Use of a Consortium-approved DSMB Charter template is required and includes the following study-specific DSMB information:

- The responsibilities of the PI, study staff, and DSMB members and support staff.
- DSMB Chair oversight, responsibilities, and replacement plan.
- Confidentiality and conflict of interest plans.
- Meeting cadence and administrative responsibilities, including minutes, distribution, and turnaround times.

- Data and information reviewed in open and closed sessions.
    - Open session data review
        - PI, study team, and study biostatistician may attend to discuss the progress of the trial.
        - Information reviewed: accrual, diversity, AEs, compliance, stopping rules, and safety reports.
    - Closed session review
        - Only DSMB members may attend.
        - Analyses of efficacy endpoints and safety data, AEs, data integrity, and risk-benefit ratios.
- For DSMBs that review randomized trials, particularly blinded trials, the charter should further describe the process by which data are provided to the DSMB and indicate whether treatment arms are distinguished or identified to the DSMB.

Studies must obtain DSMB approval to continue accrual. The PI is responsible for expeditious implementation of any changes required or recommended by the DSMB. The PI is required to submit DSMB reports to the DSMC and the IRB in a timely manner.

A DSMB may be assembled on an ad hoc basis when unexpected circumstances arise regarding safety issues in a trial without a prospectively assembled DSMB. This determination may be made by the PI, DSMC, DSMC Compliance Sub-Compliance, other oversight committee, or IRB, and may be required for the duration of a trial or for a limited period, as determined by the requesting entity. If the DSMB is required for the duration of the trial, the protocol must be amended to reflect this change and a written charter must be prepared.

<u>DSMB Review Outcomes:</u>
A DSMB assigns an outcome of full approval, conditional approval, or suspension as defined below.

- Full approval: accrual may continue, no changes required.
- Conditional approval: accrual may continue but a protocol modification and/or additional clarifications regarding data submitted are required.
- Suspension: accrual must stop until all necessary protocol changes are made; investigational treatment may continue for previously enrolled subjects (determined on a trial-by-trial basis).

Failure to hold required DSMB reviews according to the requirements in the approved protocol or failure to follow the recommendations of the DSMB, without adequate justification, will be grounds for suspending the trial by the DSMC.

Additional Reviews

Institutional Biosafety Committee (IBC):
IBC review is required for trials involving gene therapy, cellular immunotherapy, and on a trial-by-trial basis per institutional IBC policies. The committee reviews and approves research involving recombinant or synthetic nucleic acid molecule for compliance as described in the *NIH Guidelines*, as well as reviewing emergency and exposure control plans associated with research using recombinant DNA, biological hazardous materials, and infectious agents.

Human Subjects Radiation Approval Committee (HSRAC):
HSRAC review is required for all human subjects research that will expose people to radiation levels above standard-of-care imaging or therapy. This includes studies where the only research scan is at baseline or initial screening.

Adverse Event Reporting

Protocols must include a section that specifies the reporting of adverse events (AEs) and unanticipated problems. Reporting procedures must follow local IRB standards, federal regulations, and NIH and OHRP guidelines in reporting of adverse events. Minimum reporting requirements for adverse events are as follows:

- Serious adverse events (SAE)
    - DSMC: Serious adverse events reported for studies without a DSMB are reported directly to the DSMC.
    - NCI Cancer Therapy Evaluation Program (CTEP): Serious adverse events in clinical trials conducted under CTEP sponsorship or by an NCI cooperative group are reported in the CTEP- AERS system.
    - IRB: Expedited reports are submitted to the IRB when a serious adverse event related to participation in the study is unanticipated.
    - FDA: Serious adverse events in clinical trials conducted under an internally sponsored IND or IDE are submitted to the FDA in accordance with FDA reporting requirements.
- Non-serious adverse events:
    - DSMC: Non-serious events for studies without a DSMB are reported to the DSMC at least annually as required by the protocol and the DSMC.
    - NCI Cancer Therapy Evaluation Program (CTEP): Non-serious adverse events are reported to CTEP in compliance with requirements of the protocol.
    - IRB: Non-serious adverse events are reported at least annually and as required by the reviewing IRB.
    - FDA: Most frequent adverse events (in addition to most serious) are reported in the annual report to the IND as required by FDA regulations.

CRS Quality Assurance and Compliance

The CRS Quality Assurance and Education unit manages the Consortium's Monitoring Program and Audit Program. Through ongoing trial monitoring and audits, CRS ensures that investigators are meeting their responsibilities for data accuracy, safety monitoring and reporting, and that trials are conducted in accordance with GCP, 21 CFR Parts 50, 56, and 312 or 812, Consortium policies, and protocol requirements.

In all cases, the PI of the trial will have the first level of responsibility for ensuring that the protocol is conducted as approved by the SRC and IRB. The PI will ensure that the institutional and protocol DSMP is followed; that all data required for oversight of safety monitoring are reviewed and accurately reported to the IRB, a DSMB, and/or the DSMC as required; and that all adverse events are reported according to protocol guidelines and all applicable regulations.

Consortium Monitoring Program

All Consortium IITs conducted at Consortium sites, including those conducted under an internally sponsored IND/IDE, will be monitored by CRS if they are not monitored by an external entity. Ongoing study monitoring is used to confirm that trials are being conducted in a manner consistent with relevant requirements (e.g., Good Clinical Practice [GCP] guidelines; 21 CFR Parts 50, 56, and 312 or 812, where applicable; Consortium policies; and the study protocol approved by the IRB); and to ensure the quality and timeliness of the study data. The internal monitoring program ensures compliance with requirements of the IRB-approved protocol, appropriate protections of clinical trial participants, accuracy and completeness of clinical trial data, and requirements for safety reporting and clinical trial investigational product management.

In addition, all trials being conducted by Consortium members under internally sponsored INDs or Significant Risk Device IDEs must, by federal regulation, be monitored by the Sponsor for compliance with the protocol, signed agreement, and other documented requirements. Other IITs may warrant similar monitoring by the responsible investigator. Sponsors may rely on the monitoring conducted by CRS to fulfill this obligation as it applies to Consortium performance sites.

All internal monitoring activities will be carried out by a dedicated team of monitors qualified and trained by the CRS Quality Assurance team to perform these services and will be independent of the study team.

Monitoring of external performance sites is the responsibility of the Sponsor and must be consistent with the requirements of the protocol DSMP and the standards set by the CRS Monitoring Program. Internal Sponsors have three options for monitoring their clinical trial:

- Contract with CRS to perform fee-for-service monitoring of external performance sites;
- Contract with an independent, experienced, and vetted monitor; or
- Contract with a Clinical Research Organization (CRO).

Risk Stratification:

Risk level is determined by CRS prior to activation and the risk level may be increased during the conduct of the trial by the PI, CRS Compliance, DSMC or the DSMC Sub-Committee, or CROC.

Monitoring initiation and frequency are determined by risk level stratification (Tables 1 and 2) as follows:

- High risk trials: The initial monitoring visit by CRS will occur 3-6 months after the first subject has completed study treatment. If initial monitoring does not result in significant concerns per the discretion of the Compliance Sub-Committee, subsequent visits will occur approximately every 6 months while new subjects are enrolling and receiving study treatment.
- Medium risk trials: The initial monitoring visit will occur 6-12 months post-treatment of the first subject. If initial monitoring does not result in significant concerns per the discretion of the Compliance Sub-Committee, subsequent visits will occur approximately every 12 months while new subjects are enrolling and receiving study treatment.
- Low risk/exempt trials: These are not monitored by CRS.
- Single Patient INDs/IDEs or Emergency Use Protocols: These are not monitored by CRS as they are not considered research.

Monitoring frequency may be increased at the request of the PI, the Sponsor, the DSMC or DSMC Compliance Sub-Committee, or CROC. Monitoring is not required if a trial has closed to accrual and/or no new subjects were enrolled (i.e., consented and started intervention) after the most recent monitoring visit. Monitoring visits are conducted remotely. On-site visits may be conducted, if feasible, at the request of the PI or at the discretion of CRS Monitoring Program.

Table 1. Risk Stratification of Trials

Risk Level	**Definition**	**Examples**
High	Clinical trials of high complexity, high potential for toxicity to participants, or those that require a high level of administrative oversight in order to comply with regulatory requirements.	• First in Human • Phase 1 trials • Dose-finding trials • Multicenter trials • Consortium-Sponsored IND trials • Consortium-Sponsored IDE trials • Gene therapy, cellular immunotherapy, or other areas designated by NIH as high-risk
Medium	Clinical trials with potential of greater than minimal risk to participants, which do not meet the definition of high-risk trials.	• All other trials involving therapeutic interventions
Low or Exempt	Clinical trials with minimal risk to participant health or safety.	• Trials involving non-therapeutic interventions • Studies determined to be exempt by the IRB • Survey studies • Retrospective chart reviews • Blood and tissue sampling • Behavioral and observational studies

Table 2: Monitoring Components by Risk Level

Risk Level	Monitoring Frequency [a, b]	Consent Review	Eligibility and Data Review [c]
High	6 months	100% of consented participants	100% of treated participants (initial visit), 20% of treated participants (subsequent visits)
Medium	12 months	100% of consented participants	50% of treated participants (initial visit), 10% of treated participants (subsequent visits)
Low or Exempt	N/A	N/A	N/A

[a] Frequency is based on enrollment. Visits are conducted only when new participants have been consented and treated since the last monitoring visit. The monitoring visit cadence for medium risk trials may be extended up to 24 months due to monitor availability, lack of findings, etc.

[b] Review regulatory documents (including IND/IDE if applicable) included in each monitoring visit.

[c] Up to 5 subjects who have completed study therapy. If more than 5 subjects have enrolled and completed study therapy at the time of the initial monitoring visit, then 20% of additional subjects may be reviewed for high-risk studies and 10% for medium-risk studies if issues have been identified in the first five subjects reviewed. Additional subjects may be selected if serious noncompliance or other significant issues are identified.

Monitoring Reports:
For every monitoring visit, a monitoring report is provided to the PI, internal IND Sponsor (if applicable), and study team and a wrap-up meeting may be held to summarize any Major or Moderate findings upon completion of the visit.

When CRS monitors on behalf of an external PI, such as reciprocal Cancer Center monitoring, or when an external agent is provided monitoring information, executive summaries will be provided in lieu of the full report. The executive summary will be provided to the study team for distribution to the external party.

CRS monitoring reports are confidential and may not be disseminated to external parties without written approval by the Fred Hutch Office of General Counsel, the University of Washington School of Medicine's Compliance Office, and/or the Seattle Children's Compliance Office.

Monitoring Outcomes:
The CRS Compliance team is responsible for reviewing all monitoring reports and a summary report is provided to the Compliance Sub-Committee as described in the Compliance Sub-Committee section. Any Major or Moderate monitoring report finding that may impact safety is escalated to the DSMC and the Compliance Summary Report that includes recommendations from the Compliance Sub-Committee is reviewed by the DSMC. Serious or continuing noncompliance and any unanticipated problems involving risks to subjects or others be submitted to the IRB on an expedited basis per IRB policy.

Every protocol monitoring visit report includes findings that are categorized according to the FDA's most common inspection observations and graded Major, Moderate, or Lesser, defined as the following:

- Major: Findings that can't easily be corrected. Corrective and Preventive Action (CAPA) plan and/or IRB reporting may be needed. Examples: patient safety concerns, missed visits, not

following protocol, question about eligibility documentation, patient signed consent but missed opt-in question.
- Moderate: Findings that can be corrected, don't violate human subjects protections, no risk of harm or safety. Example: data discrepancies.
- Lesser: Findings that may not impact the quality of the trial or participant safety, but do not follow Consortium standards or best practice.

Follow-up Requirements:
All monitoring findings must be resolved according to the specified timeframes outlined below.
- Urgent Action Items: Major findings related to significant noncompliance, participant safety, eligibility, SAE reporting, or consent are marked 'urgent' and need to be addressed within 10 days.
- Priority Action Items: Major findings related to insufficient AE reporting, IND-related communications/submissions, or outstanding monitoring findings are marked 'priority' and need to be addressed within 30 days.
- Action Items: Moderate or Lesser findings must be addressed by the next monitoring visit.

Consortium Audit Program
All Consortium trials are subject to internal audit by the CRS Compliance program and internal audits are performed independently of the Consortium Monitoring Program. Consistent with the Consortium Monitoring Program monitors, auditors are not directly involved in the conduct of clinical trials and are not considered a member of the study team.

The purpose of a quality assurance audit is to ensure appropriate protections of clinical trial participants and compliance with the requirements of the IRB-approved protocol, including requirements for safety reporting and investigational product management. The compliance team conducts three types of audits: (1) High Risk Audits, (2) Routine Audits, and (3) Focused Audits. Consortium IITs are the primary focus of internal audits, but audits are also performed on national cooperative group and industry sponsored trials. Audits are typically conducted without study team involvement to provide a real-time snapshot of the health of the study and ensure the study is "audit-ready". A re-audit of any trial may occur where major findings were identified. This is done after sufficient time has allowed for the accrual of new subjects and performed using the focused audit approach.

- High risk audits are conducted on all first-in-human and other high-risk IITs within three months post-treatment of the first subject enrolled and focus on review of the informed consent process, subject(s) eligibility and initiation of protocol-specified treatment, IP administration according to protocol specifications, and evaluation of subject safety.
- Routine audits may be conducted on any trial type but are focused on IITs and national cooperative group trials to ensure the quality of the Sponsor's monitoring and oversight of study conduct. Typical areas of review include regulatory documentation, IND/Significant Risk IDE documentation, informed consent forms, test article inventory, and safety reports. Protocols are selected for routine audit across each research group and using a risk-based algorithm generated by OnCore CTMS. At least one protocol is selected for routine audit per month. Routine audits are also conducted for manufacturing facilities that support IITs and when a study team identifies the potential for a routine FDA inspection based on a sponsor

filing a commercial application with FDA (New Drug Application, Biologics License Application, or supplemental NDA/BLA).

- Focused audits are conducted on any clinical trial type with a known or suspected deficiency. Focused audits may be performed in response to a monitoring report or trend observed across more than one monitoring report; a report from an outside auditor or inspector; or a request from the PI, DSMC or Compliance Sub-Committee, CROC, NCI, IRB, or clinical trial sponsor. Factors that may trigger a focused audit include, but are not limited to, suspected inadequacies in clinical trial management, large numbers of serious adverse events, an excessive number of protocol deviations, delayed submission of required reports to the IRB and/or FDA, high staff turnover, or IRB findings of serious and continuing noncompliance. Focused audits may review all aspects of the study or target a specific audit category. Based on review of external monitoring reports, CRS may conduct focused audits for industry sponsored trials.

Audit Outcomes

For all audit types, an audit report is generated, and assigned one of the following outcomes:

- Outstanding
- Acceptable
- Acceptable with follow-up, or
- Unacceptable.

All audit outcomes are reviewed by the Compliance Sub Committee and reported to DSMC as part of the Compliance Summary Report (CSR). Identification of serious or continuing noncompliance and any unanticipated problems involving risks to subjects or others will be communicated to the PI, study team, and DSMC immediately and reported to the IRB per IRB policy. An Unacceptable audit outcome requires a PI response letter and formal CAPA and is reported directly to the DSMC for ad hoc review. For Acceptable with Follow-Up audits, a PI response letter is required and will be reported directly to the DSMC if there are any patient safety related concerns. Failure to meet response requirements results in escalation to the DSMC. Any audit or deficient audit response may be escalated directly to CROC. If the audit results in an outstanding or acceptable outcome, no further action by the PI is required.

The DSMC and CROC have the authority to suspend or close a study or impose other requirements or sanctions on the PI or research program as a result of an audit outcome. If the DSMC or CROC make this determination, the IRB will be notified of any suspension, closure, or sanctions.

Protocol Suspension or Termination

When protocols are suspended or terminated, the Principal Investigator is responsible for notifying applicable stakeholders.

Notifying Federal Agencies of Suspensions and Closures
Suspensions or termination/closure of research trials that results from the actions of the FDA, IRB, or any of the above-mentioned institutional oversight bodies, including the SRC, DSMB, DSMC, or CROC, will be promptly reported to all government departments and agencies that are legally required to receive such a notification, including the NCI Program Director responsible for funding the trial, if applicable.

Notifying Sponsors of Suspensions and Closures
Suspensions or termination/closure of research trials should be promptly reported to the Sponsor, in accordance with the requirements specified in the clinical trial agreement.

Conflict of Interest

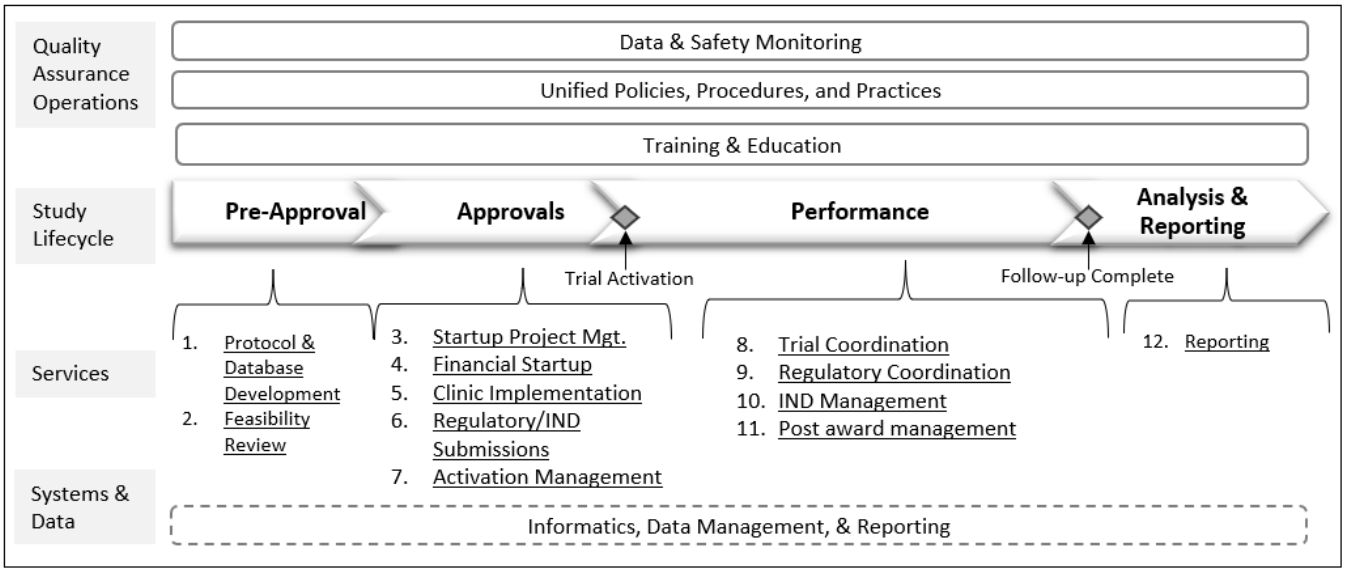
All Consortium investigators are obligated to follow institutional policies with respect to financial conflict of interest (COI) and human subject research activity. The procedures for disclosure and management of financial conflict of interest, as well as procedures for ensuring compliance therewith, are specific to each institution and are implemented outside the scope of this DSMP. Prior to IRB approval, each institution provides assurance that the trial has met the institutional financial conflict of interest requirements. Through these mechanisms, Consortium committees are assured that issues related to potential financial COI have been appropriately addressed prior to submission for review. Once a submission is made, Consortium committees manage COI within their review process and these procedures are found in individual committee's COI Guideline documents.

The following are financial conflicts of interest. Financial interest accruing to immediate Family Members of a Covered Person (spouse, domestic partner, or dependent child of a Scientific Staff member) must be considered as a financial interest of the Covered Person.

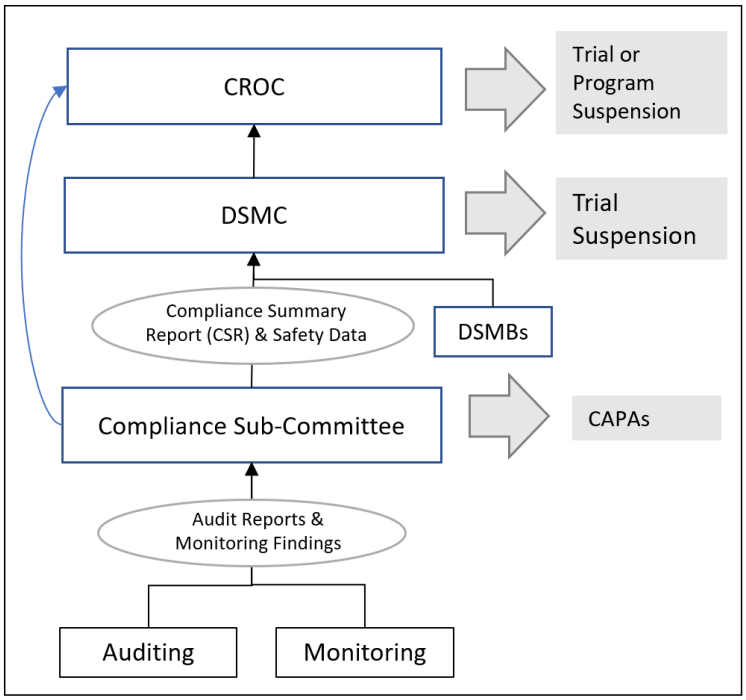
Financial Conflict is a financial interest that could affect or be affected by the outcome of the research protocol under review, as defined by any of the following:

- Equity interest (e.g., stock; stock options or other ownership interests) of more than $5,000 in a publicly traded entity, or an equity interest of any amount in a not publicly traded entity
- Payments derived from intellectual property rights (e.g., patent royalties)
- Payments received for consulting or other services (e.g., salary, honoraria, and fees) in the prior calendar year or expectation of future payments or benefits in the next 12 months of more than $5,000.

APPENDIX A: CLINICAL RESEARCH SUPPORT (CRS) SERVICES AND CLINICAL TRIAL LIFECYCLE



APPENDIX B: CONSORTIUM DSM FUNCTIONS AND ESCALATION PATHWAYS



APPENDIX C: COMMITTEE ROSTERS

RESEARCH DISEASE & MODALITY GROUPS
The current Research Group membership roster is available on the Cancer Consortium site:
Research Group Review (cancerconsortium.org)

SCIENTIFIC REVIEW COMMITTEE ROSTER
The current SRC membership roster is available on the Cancer Consortium site:
Scientific Review Committee (cancerconsortium.org)

DATA AND SAFETY MONITORING COMMITTEE (DSMC) ROSTER
The current DSMC membership roster is available on the Cancer Consortium site:
Data and Safety Monitoring Committee (cancerconsortium.org)