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U.S. Department of Health
and Human Services
National Institutes of Health

November 5, 2021

Thomas J. Lynch, M.D.
Cancer Center Director

Fred Hutch/University of Washington Cancer Consortium
Seattle, WA 98109

Dear Dr. Lynch:

The Fred Hutch/University of Washington Cancer Consortium Data and Safety Monitoring Plan (2021_v5.0) submitted for NCI review is approved. Please retain this letter for your records.

Sincerely,

Min He
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FRED HUTCH / UNIVERSITY OF WASHINGTON

CANCER CONSORTIUM

INSTITUTIONAL DATA AND SAFETY MONITORING PLAN

Responsible Official: Thomas J. Lynch, Jr., MD; Cancer Center Director
Responsible Office: Office of the Director

Signature of the Cancer Center Director: Tom Lynch

Current version: 5.0
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Contents

1.0 INTRODUCTION AND OVERVIEW

This Data and Safety Monitoring Plan (DSMP) covers human subjects research conducted under the auspices of the Fred Hutch/University of Washington Cancer Consortium (hereafter referred to as the Consortium), comprising three academic partners, Fred Hutch, UW Medicine (UW), and Seattle Children's (SC), plus an outpatient clinic and major site of clinical research practice, the Seattle Cancer Care Alliance (SCCA), on the Fred Hutch campus. From 1976 – 2002, the Fred Hutch alone was an NCI designated comprehensive cancer center, and the DSMP was approved by NCI October 25, 2001. During the development of the Consortium, the Fred Hutch DSMP was modified to include Consortium partners. Subsequent refinements have been made to the plan based on best practice and changes in NCI guidelines.

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

The broad scope of this plan includes all research trials subject to scientific review under the Consortium's Protocol Review and Monitoring System (PRMS), including all cancer-related trials involving human subject intervention 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, such as pharmaceutical companies and recognized national cooperative groups.

2.0 DEFINITIONS

Ancillary or Correlative:

- Ancillary: Studies that are stimulated by, but are not a required part of, a main clinical trial/study, and that utilize patient or other resources of the main trial/study to generate information relevant to it. Ancillary studies must be linked to an active clinical research study and should include only patients accrued to that clinical research study. Only studies that can be linked to individual patient or participant data are reported.
- Correlative: Laboratory-based studies using specimens to assess cancer risk, clinical outcomes, response to therapies, etc. Only studies that can be linked to individual patient or participant data are reported.

Cancer-related trial: A trial that either directly involves cancer patient research, research of secondary conditions related to cancer treatment, or research related to cancer prevention.

Externally Peer-Reviewed: R01s, SPORES, U01s, U10s, P01s, CTEP, or any other clinical research mechanism on this list:
http://cancercenters.cancer.gov/documents/PeerReviewFundingOrganizations508 C.pdf

Industrial Trials: A pharmaceutical, device, or biotechnology company controls the design, and implementation of these clinical research trials. The company also provides funding to support the trial.

Institutional (Investigator-Initiated) Trials: In-house clinical research trials authored or co-authored by Cancer Center investigators and undergoing scientific peer review solely by the Protocol Review and Monitoring System (PRMS) of the Cancer Center. The Cancer Consortium investigator has primary responsibility for conceptualizing, designing, and implementing the clinical research trial and reporting results.

- It is acceptable for industry and other entities to provide support (e.g., drug, device, other funding), but the trial should clearly be the intellectual product of the Center investigator
- This category may also include:
    - Institutional trials authored and implemented by investigators at another Center in which the Consortium is participating
    - Multi-Institutional trials authored and implemented by investigators at the Consortium (Note: National and externally peer-reviewed trials are not Institutional trials)

Internally Sponsored IND/IDE: An Investigational New Drug (IND)/Investigational Device Exemption (IDE) held by a Consortium investigator or a Consortium institution.

Interventional trial: Individuals are assigned prospectively by an investigator based on a protocol to receive specific interventions. The participants may receive diagnostic, treatment, behavioral,

or other types of interventions. The assignment of the intervention may or may not be random. The participants are followed and biomedical and/or health outcomes are assessed.

Minimal risk trial: A trial for which the anticipated risks are no greater than those ordinarily met in daily life, or during the performance of routine physical or psychological examinations (e.g., blood draw, urine sample, anonymous survey, surveys that are not used for patient care or outcomes).

National Cooperative Group Trials: These are trials supported by the NCI National Clinical Trials Network (NCTN) or other NIH-supported National Trial Networks (Nationally funded Consortiums).

Observational: Studies that focus on cancer patients and healthy populations and involve no prospective intervention or alteration in the status of the participants. Biomedical and/or health outcome(s) are assessed in pre-defined groups of participants. The participants in the study may receive diagnostic, therapeutic, behavioral, or other interventions, but the investigator of the observational study is not responsible for assigning specific interventions to the participants of the study.

Treatment: Trial designed to evaluate one or more interventions for treating a disease, syndrome, or condition. Note: This equates to therapeutic trials in previous versions.

3.0 OVERSIGHT AND ORGANIZATION

3.1 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 CROC has the following functions:

- Reviews 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 SRC and the Data and Safety Monitoring Committee (DSMC).
- Provides regular updates to leaders and staff of their institutions.
- The CROC does not review SRC decisions, nor does it review clinical trials for scientific merit or accrual.

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. Committee membership includes the Consortium Associate Director for Clinical Research, the Fred Hutch Sr. VP for Clinical Research, the UW Chief of Medical Oncology, the Consortium Associate Director for Solid Tumor Research, the Seattle Children's Associate Division Chief for

Hematology/Oncology, the SCCA Medical Director, and 1-2 Consortium members with clinical research programs.

3.2 Clinical Research Support (CRS)

The implementation and oversight of the DSMP is provided by the Consortium's CRS office. The Director of CRS works in partnership with the CRS Medical Director to ensure implementation of this plan. Responsibilities are as follows:

- Provide administrative support to the SRC, which is responsible for scientific review, feasibility, and scientific progress (fulfilling Cancer Consortium Support Grant PRMS functions), and the DSMC.
- Monitor Consortium investigator-initiated trials that are not externally monitored.
- Perform routine and focused audits of clinical trials as described in this document.
- Review the DSMP of all new investigator-initiated protocols for consistency with the Consortium DSMP.
- Train investigators and clinical trial staff in the development and conduct of clinical research.
- Recommend Consortium-wide policies and procedures for clinical trials and develop strategy for implementation with oversight and support from the CROC.

3.3 Research Groups

Groups of investigators are organized around specific disease and modalities with ongoing clinical trials and each group has an appointed leader. The groups oversee evaluation of clinical trials during their development and assess feasibility based on scientific merit, interest of the members, availability of the needed patient population and overlap with current research group portfolio, available resources, and importance to the catchment area, the 13 counties of Western Washington that are included in the Surveillance, Epidemiology, and End Results Program. These groups monitor their research portfolio and assess accrual within the group.

New interventional, cancer-related trials must have documented reviews approved by the appropriate Research Group(s) if they will recruit subjects within the Consortium.
The Research Group Review informs the SRC on how competing trials will be managed. The Research Group Review must be completed prior to submission to SRC for scientific review and includes an operational priority score that ensures prioritization of research efforts and resource allocation. This priority score impacts submissions for SRC agenda placement. Prioritization is included with all protocols submitted to SRC (not required for expedited or exempt protocols). The Research Group Review may determine a study is not feasible if there are substantive issues and disapprove moving forward to SRC.

3.4 Scientific Review Committee (SRC)

This committee provides a formal internal scientific peer-review process for applicable cancer-related protocols. 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 and monitoring functions.

SRC Membership

Committee members are appointed by the Cancer Center Director; appointment is renewable. The committee has a defined membership representing all of the major clinical research areas of the Consortium. A CRS representative serves as non-voting ex-officio member of the SRC.

SRC New Protocol Review:

SRC reviews new protocols for the following:

- Scientific merit
- Research design (including biostatistics)
- Feasibility of achieving accrual goal given other accruing trials and the available patient population where competing trials are of concern.

Full committee protocol review consists of a scientific, statistical, administrative, and ad hoc reviews as needed. A quorum is required to convene the meeting, and to achieve a quorum, the presence of eight core SRC members, including a biostatistician, is required. Ad hoc members may vote, but they do not contribute to the calculation of quorum.

Two reviewers and a biostatistician are assigned to review each protocol. Only the SRC Chair and administrative staff are aware of the reviewer assignments prior to the meeting to support independent reviews.

The administrative review determines the availability and completeness of DSMPs for relevant protocols before the SRC meeting. Protocols with insufficient DSMPs will not be approved by the SRC. Requirements for DSMPs are described in this document.

Biostatisticians review the statistical design to ensure that the following key criteria are met for each study:

- Statement of scientific rationale and hypothesis for the study
- Statement of study objectives
- Description of the study design, including Phase and randomization features
- Statement and or definition of study outcomes and or endpoints to be evaluated
- Some type of justification for the sample size is required for each study.
    - Phase II & III protocols, biostatisticians review to confirm appropriate power calculations. This may not be relevant for some Phase II designs.
    - Phase I protocols require a description and rationale of the design
- Description of how the data will be analyzed - at minimum for the primary objective, preferable for all primary and secondary objectives

Expedited Review: Trials under the purview of SRC that do not require full committee review are granted expedited reviews conducted solely by the SRC Chair. Those trials that may have an expedited review include NCTN trials, extension trials, trials that were specifically peer-reviewed by NCI mechanisms and multi-site trials that have been reviewed by the PRMS of another Cancer Center with an NCI fully- approved PRMS. SRC Chair expedited reviews consider the same documents reviewed by the full SRC.

- Exempted from Review: Observational and Ancillary-Correlative studies are administratively reviewed and exempt from full and expedited SRC review. Compassionate Use and Expanded Access protocols are also exempt from review since these protocols are not designed to answer formal scientific questions.

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

Protocol Amendments Requiring SRC review

To ensure scientific merit throughout the life of the clinical trial, administrative and scientific reviews are conducted for applicable protocol amendments. Changes that affect local accrual totals for trials are reviewed administratively to update the database and ensure accurate accrual monitoring.

Institutional and Externally Peer-Reviewed trials subject to full SRC review as a new protocol may require full SRC review for amendments that significantly alter the research design or resources, 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 as these changes have been thoroughly reviewed for scientific merit outside of the Consortium. SRC does not review amendments for that qualified for expedited review for the initial review.

In addition, the SRC does not review amendments for trials which are permanently closed to accrual locally, unless a Consortium site serves as the coordinating center for a multicenter trial still open to accrual at another site.

SRC Review Outcomes:

Feedback is provided to the Principal Investigator. Outcomes for the protocol review include:

- Full approval
- Conditional approval (not applicable for industry-sponsored trials)
- Disapproval

Monitoring Ongoing Scientific Progress

The SRC also provides oversight of applicable trials open to subject enrollment. This oversight includes 1) review of the continued scientific merit of the research and 2) the progress of the protocol in achieving its targeted accrual rate (see description below).

Targeted and actual accrual is reviewed annually based on the Low Accrual Policy. *The SRC has authority to close a trial to further accrual with treatment, intervention, and subject follow-up continuing.*

3.5 Institutional Review Board (IRB)

The IRB reviews research activities involving human subjects to ensure that ethical standards for the care and protection of human subjects have been established and are in compliance with all pertinent regulations (federal, state, and local) and Consortium policies. *An Institutional Review Board (IRB) must approve the protocol before activation. At any time, subsequent to activation, the IRB may require additional changes to the protocol.*

The Fred Hutch IRB functions as the Cancer Consortium's IRB (CCIRB). The CCIRB will serve as the single IRB (sIRB) for multi-site trials and will likewise rely on other IRBs when appropriate. Prior to submission to an external IRB, the Institutional Review Office (IRO) reviews and endorses the external IRB submission. Industry-sponsored trials may be reviewed by WIRB Copernicus Group IRB (WCGIRB).

IRB Continuing Review

All trials are required to obtain re-approval by the IRB no less than annually to continue accrual, continue intervention if accrual is complete, and/or to analyze data. The IRB makes an independent assessment of the progress and safety of the trial and determines whether the perceived risk-benefit ratio continues to be acceptable. The IRB has the authority to suspend or terminate trials that no longer demonstrate an appropriate risk-benefit ratio or that are otherwise not conducted in compliance with the IRB approved protocol.

3.6 Data and Safety Monitoring Committee (DSMC)

The Consortium DSMC ensures participant safety and reviews applicable cancer-related trials. initially reviewed by SRC are subject to annual DSMC review if the intervention involves a drug, device, or biologic. The highest level of review is given to investigator-initiated trials without a DSMB. The DSMC does not oversee clinical trials monitored by another entity including national cooperative group trials monitored by a DSMB and industry-sponsored clinical trials.

DSMC Membership

The CROC recommends members, and the Cancer Center Director appoints members of the DSMC. The DSMC membership does not overlap with SRC membership and includes representation from solid tumor, hematology, and biostatistics. The term of membership is renewable by the Cancer Center Director.

DSMC Continuation Review

In general, the DSMC meets every other week to conduct annual reviews of trials. Additional meetings may be convened to address urgent concerns. The DSMC reviews trials that have been

opened to accrual and have accrued at least one subject. DSMC is not required if a trial has permanently closed to accrual and no subjects were enrolled or received study treatment in the previous year.

A quorum is required to convene the meeting, and to achieve a quorum, the presence of four DSMC members, the DSMC Chair plus three members, is required and all decisions must be unanimous. Each trial is assigned to one reviewer.

The DSMC reviews as follows:

For trials without a DSMB, the DSMC will review the following current information:

- Number of subjects
- Unanticipated Problems
- Serious Adverse Events
- Stopping rules, if applicable
- List of dose-limiting toxicities and responses that have occurred in the specified timeframe
- A cumulative tabulation of adverse events by type and grade, including deaths, as described by the protocol DSMP

For trials with a DSMB, the DSMC will review:

- Number of subjects
- Unanticipated problems
- Serious Adverse Events
- The DSMB report will be reviewed with regard to accrual, stopping rules, if applicable, adherence to the protocol DSMP and scheduled reviews, together with any recommendations by the DSMB.

<u>DSMC Outcomes:</u>

- Full Approval: Accrual may continue, no changes required
- Full Approval: No changes required (if treatment continues but trial is closed to accrual)
- 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
- Closure: Accrual must stop, and investigational treatment must be discontinued for previously enrolled subjects.

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 or closing the trial by the DSMC.

Outcome of the DSMC review is communicated promptly to the Principal Investigator and then reported if appropriate to the IRB by the PI. The PI has the opportunity to respond to any of

DSMC's concerns, which are then reviewed by the full committee or the original reviewer and Chair as appropriate.

3.7 Compliance Sub-Committee

Quality assurance responsibilities are managed by CRS Regulatory Affairs and Compliance and overseen by the Compliance Sub-Committee, which functions under the direction of the CROC. The Compliance Sub-Committee operates under a strict confidentiality agreement.

The Compliance Sub-Committee has two primary responsibilities: 1) identification of significant compliance issues and 2) ensuring adequacy of the monitoring plan for external performance sites associated with Consortium investigator-initiated trials. The group is composed of the CRS Medical Director, Assoc. Vice President of CRS, and the CRS Director of Regulatory Affairs and Compliance.

CRS Regulatory Affairs and Compliance staff reviews all monitoring and auditing reports; those with issues impacting subject safety or serious, persistent noncompliance are escalated to the CROC. In addition, CRS conducts a prospective review of all monitoring plans for external performance sites for Investigator-Initiated trials and monitors the protocol regulatory file during the conduct of the trial to determine compliance with the approved plan. The Consortium ensures that the conduct of clinical research is consistent with all applicable regulations, and guidance, including reporting of adverse events to the IRB, sponsors, OHRP, and FDA, as required.

In general, the Compliance Sub-Committee meets monthly to review the compliance of all ongoing clinical research. Additional meetings or communication may occur to address urgent concerns.

3.8 Data and Safety Monitoring Boards (DSMBs)

Any and all members must not have any part in the design, conduct, or reporting of the clinical trial. In most circumstances, at least one member of the DSMB should be independent of the Consortium institution conducting the trial.

For DSMBs that review randomized trials, particularly blinded trials, a written charter should be established outlining the responsibilities of the PI, study staff, and DSMB with respect to the nature of the data to be reviewed. The charter should cover the process by which data are provided to the DSMB and indicate whether treatment arms are distinguished or identified to the DSMB. Generally, the minimal disclosure necessary for the DSMB to carry out its agreed responsibilities is encouraged.

Studies must obtain DSMB approval to continue accrual. In addition, 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. Such a request may be made by the PI, DSMC, or IRB. If the DSMB will continue to review the trial on a routine basis, the protocol will be amended to reflect

this change. CRS may provide administrative meeting minutes support for regularly scheduled and ad hoc DSMB meetings.

4.0 ADDITIONAL REQUIREMENTS

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 Deoxyribonucleic Acid (DNA) Molecules. Specifically, Phase I and II gene transfer trials must comply with additional requirements imposed by the latter NIH guidelines.

5.0 PROTOCOL DATA AND SAFETY MONITORING PLANS (DSMP)

Protocols must incorporate in their design a DMSP appropriate for the potential risks and size of the trial.

The following minimum guidelines for safety in the trial design will apply:

- For all trials, investigators conduct continuous review of data and subject safety. The review for each dose level will include the number of subjects, significant toxicities as described in the protocol, dose adjustments, and responses observed.
- Phase I trials must clearly define dose limiting toxicities, rules for escalation of dose, and criteria for stopping the trial and defining the Maximum Tolerated Dose.
- Phase II 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 most randomized Phase II and Phase III trials, particularly those that are blinded or multi- institutional, a study-specific Data and Safety Monitoring Board (DSMB) will be required to review safety and other data at pre-specified intervals, and at least annually.
- A trial-specific DSMB may be required for other trials, particularly for investigator-initiated Phase I or Phase II trials involving multiple institutions, unusually high-risk interventions (such as gene therapy or cellular immunotherapy), or unusually vulnerable populations.
- Institutional Biohazard Committee (IBC) review is required for trials involving gene therapy, cellular immunotherapy, and on a trial-by-trial basis per institutional IBC policies.
- 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.
- 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.

- 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 at outside sites. The trial PI may delegate some or all of these responsibilities to appropriately trained staff, but the trial PI maintains ultimate responsibility. 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.
- 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.
- CRS Regulatory Affairs and Compliance will review the monitoring plan for external performance sites to ensure consistency with the Consortium DSMP. A new protocol must receive DSMP approval before it can proceed to SRC review.
- The PI is required to submit DSMB reports to the DSMC and the IRB in a timely manner.

6.0 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 to the DSMC at least annually.
    - 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 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 to the IRB in accordance with the DSMP outlined in the protocol at least annually 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.

As part of its routine responsibilities, the IRBs receive expedited reporting of unanticipated problems and unexpected adverse events related to participation in the study, on a continuous basis. These expedited reports are reviewed by the IRB Chair or designee, along with a history of other unanticipated problems and unexpected adverse events associated with the trial. If the IRB Chair or designee determines that the report does not describe an unanticipated problem or unexpected AE involving risk to subjects or others, the result is noted in the IRB file for the research protocol. Otherwise, the report is referred for full review by the convened IRB. The IRB Chair or designee will determine whether an emergency meeting of the IRB is necessary or whether the IRB review can occur at the next scheduled meeting of the convened IRB.

7.0 GUIDELINES FOR DATA AND SAFETY MONITORING IMPLEMENTATION

Overview: Requirements for Monitoring and Reporting

The Consortium has a system to ensure that investigators are in compliance with their responsibilities for data accuracy and safety monitoring and reporting. Together with investigators**,** CRS is responsible for:

- Monitoring all approved clinical trials that have limited or no external safety oversight in accordance with the CRS Monitoring Program
- Auditing in accordance with the CRS Auditing Program

Primary Responsibility for Safety and Accuracy

In all cases, the PI of the study 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 DSMP is followed; that all data required for oversight of monitoring are 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.

Trials are classified by level of risk, which determines the level of monitoring that occurs while the trial is ongoing.

Risk Stratification

Internally sponsored IND/Significant Risk Device IDE trials and all types of trials designated as high risk by the NIH must remain in the "High risk" level. The risk level of other trials may be adjusted by the SRC or IRB. Intervention trials cannot be classified as "Exempt". The proposed risk level is considered administratively and approved as part of the review process. Substantive changes to the research during the conduct of the study may impact the risk level designation.

Table 1. Risk Stratification of Trials

Level of Risk	Definition	Examples
High	Clinical trials of high complexity, high potential for toxicity to participants, or those that require a high level of administrative oversight	• Phase I studies • Dose-finding studies • Multi-site studies • Consortium-Sponsored IND studies • Consortium-Sponsored IDE studies • 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	Clinical trials with minimal risk to participant health or safety	• Trials involving non-therapeutic interventions
Exempt	Non-interventional or minimal risk studies studies determined to be exempt by the IRB of record	• Survey studies • Retrospective chart reviews • Blood and tissue sampling • Behavioral and observational studies

7.1 Consortium Monitoring Program

All trials being conducted by Consortium members under internally sponsored INDs/Significant Risk Device IDEs must, by federal regulation, be continuously monitored by the Sponsor. Other internally-sponsored trials may warrant similar continuous monitoring by the Sponsor.

In addition, all Consortium investigator-initiated studies, including those conducted under an internally sponsored IND/IDE, that are treating subjects at Consortium sites will be monitored by CRS if they are not monitored by other entities. These internal monitoring visits have two purposes, first 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; and the study protocol approved by the IRB) and second, to ensure the integrity 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. 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. This option is dependent on available CRS monitoring resources.
- Contract with an independent, experienced monitor.
- Contract with a Clinical Research Organization (CRO).

If an internal Sponsor contracts with an independent monitor or clinical research organization (CRO), CRS will not monitor the trial.

Monitoring frequency is determined by risk level stratification (Table 1) as follows:

1. High risk trials: The initial monitoring visit by CRS will occur no later than 6 months after the first subject has completed study treatment. Subsequent visits will occur approximately every 6 months while new subjects are enrolling and receiving study treatment. Monitoring is not required if a study has closed to accrual and/or no new subjects were enrolled (i.e. consented and started intervention) after the most recent monitoring visit.
2. Medium risk trials: Monitoring visits will occur every 12-24 months while new subjects are enrolling and receiving study treatment. Monitoring is not required if a study has closed to accrual and/or no new subjects were enrolled (i.e. consented and started intervention) after the most recent monitoring visit.
3. Single Patient INDs/IDEs or Emergency Use Protocols: These are not monitored by CRS as they are not considered research.

The internal monitoring activities will be carried out by CRS Regulatory Affairs and Compliance staff or by external monitors who are contracted by CRS. Each monitor will be qualified and trained by CRS Regulatory Affairs and Compliance to perform these services and will be independent of the study team. CRS will maintain files of resumes and institutional training records of individuals performing monitoring activities.

Clinical trials are reviewed according to the following schedule (Table 2):

Table 2: Auditing and Monitoring by Risk Level						
	Auditing				Monitoring	
	Monitor Visit	Consent Document Review	Critical Document Review	Test Article Inventory	Eligibility Review	Data Review
Risk Level	**Frequency (months)**	**Cases (%)**	**Frequency (months)**	**Frequency (months)**	**Cases (%)**	**Cases (%)**
High	6 mos.*	100	6 mos.	6 mos.	100** (1st visit), 20***	100**(1st visit), 20***
Medium	12-24 mos.	100	12-24 mos.	12-24 mos.	50**(1st visit), 10***	50**(1st visit), 10***
Low or Exempt	N/A	N/A	N/A	N/A	N/A	N/A

*High risk studies may be reviewed annually if no subjects enrolled since the previous monitoring visit.

**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 first 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.

***If this percent is more than 3 subjects, a minimum of 3 will be reviewed. If 3 or fewer subjects have been enrolled since the last visit, all will be reviewed. Additional subjects may be selected if serious noncompliance or other significant issues are identified.

Monitoring Findings

At the completion of the monitoring visit, and before the creation of the visit report, a meeting may be held to summarize any significant findings with the PI and appropriate study personnel. Reports are provided to the PI, internal IND Sponsor (if applicable), and study team within four weeks of a monitoring visit. CRS Regulatory Affairs and Compliance will review all monitoring reports under the direction of the Director. As necessary, these reports will be referred to the appropriate group within CRS Regulatory Affairs and Compliance who will assist the PI and study team in creation of corrective and preventive action (CAPA) plans with required responses and deadlines. Summary reports will be provided to the Compliance Sub-Committee as described in the Compliance Sub-Committee section.

The CRS Compliance Manager or designee will escalate issues from the monitoring reports to the Compliance Sub-Committee as necessary and may also require that reports of 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.

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.

7.2 Consortium Auditing Program

The purpose of a quality assurance audit is to ensure compliance with the requirements of the IRB-approved protocol, appropriate protections of the clinical trial participants, and requirements for safety reporting, and investigational product management. CRS conducts audits of investigator- initiated clinical trials. Based on review of external monitoring reports, CRS may conduct focused audits for Industry sponsored studies.

CRS Regulatory Affairs and Compliance staff will oversee either internal or external staff in the conduct of audits. Auditing team members will not be directly involved in the conduct of the clinical trial.

Audit Types

The audit program is divided into two categories: routine audits and focused audits.

- Routine audits are conducted for investigator-initiated clinical trials to ensure the quality of the Sponsor's monitoring/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. These audits are typically performed in conjunction with routine monitoring visits.
- Focused audits are conducted on a clinical trial with a known or suspected deficiency. Targeted audits may be made in response to a monitoring report or a report from an outside auditor or inspector, or at the request of the PI, DSMC, NCI, IRB, or a clinical trial's sponsor. Factors that may trigger a targeted 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, late submission of IRB continuing review information, or IRB finding of serious and continuing noncompliance. Focused audits may review all aspects of the study or target a specific audit category.

Audit Findings

At the completion of the audit visit, and before the creation of the visit report, a meeting may be held to summarize any significant findings with the PI and appropriate study personnel. CRS Regulatory Affairs and Compliance, in collaboration with the PI and research team, may assist in the creation of corrective and preventative action (CAPA) plans and required responses with deadlines. Findings may also result in recommendations to be implemented at the discretion of the PI before the next audit.

Full reports are provided to the PI, study team, and Consortium Sponsor-Investigator where applicable within four weeks of an auditing visit. CRS Regulatory Affairs and Compliance will review all audit reports and escalate issues to the Compliance Sub-Committee as necessary. CRS may also require that reports of serious or continuing noncompliance and any unanticipated

problems involving risks to subjects or others be submitted by the PI to the IRB on an expedited basis per IRB policy. The PI may respond to Compliance Sub-Committee findings and determinations; the CROC may review Compliance Sub-Committee findings. The CROC has authority to suspend or close a study or impose other requirements or sanctions on the PI. If the CROC makes these determinations, the IRB will be notified of any suspension, closure, or sanctions.

Notifying Federal Agencies of Suspensions and Closures

Suspensions or termination/closure of research that results from the actions of the FDA, IRB, SRC, DSMB, DSMC or CROC based on subject safety or protocol compliance issues 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.

8.0 CONFLICT OF INTEREST (COI)

All Consortium investigators are obligated to follow institutional policies with respect to financial conflict of interest 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, the Research Groups, SRC, and DSMC are assured that issues related to potential financial COI have been appropriately addressed.

The SRC and DSMC ensure members do not participate in the review or voting process for trials in which a financial or non- financial conflict exist for Covered Persons. The Research Groups ensure Directors or designees do not serve as signatory for the approval of new protocols in which a financial or non- financial conflict exist. Covered Persons are SRC and DSMC members and Chairs, and Research Group Directors or designees. 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. It is the guideline of the Research Groups, SRC, and DSMC that all potential financial and non-financial conflicts of interest must be self-identified to the best of the individual's knowledge and appropriately managed to prevent such conflicts from interfering with the objectivity and validity of the review process. The Research Groups, SRC, and DSMC do not require disclosure of the nature of the conflict.

The following are financial and non-financial conflicts of interest that exclude Covered Persons from participating in the SRC and DSMC review process or serving as signatory for the Research Group Review approval of a new protocol.

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.

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
- 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

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

- Principal Investigator of the protocol under review by the DSMC
- Sub Investigator of the protocol under review by the DSMC
- Biostatistician involved in design of the protocol under review by the DSMC

Procedures for identification of Conflicts of Interest and Recusal of certain Covered Persons

- When the Covered Person with a conflict of interest is a Research Group Director, a designee without a conflict will be appointed to complete the Research Group Review and sign the Research Group Review Summary Form for that review. If the Principal Investigator signs the Research Group Review Summary Form, the SRC will reject the submission. The RGR and Summary Form must be redone as required by guidelines above.
- All SRC and DSMC members must notify the Chair and/or designee of a potential conflict of interest prior to the scheduled meeting. If the member is uncertain if a potential conflict of interest exists, they are encouraged to consult with the Chair and/or designee.
- If a SRC or DSMC member is assigned a review and a conflict of interest exists, the member must notify the Chair and/or designee as soon as possible. Once a conflict of interest is confirmed, the review will be reassigned to another non-conflicted reviewer.
- At the beginning of each meeting, SRC and DSMC members will be asked to declare the existence of any previously undisclosed conflicts but are not required to describe the

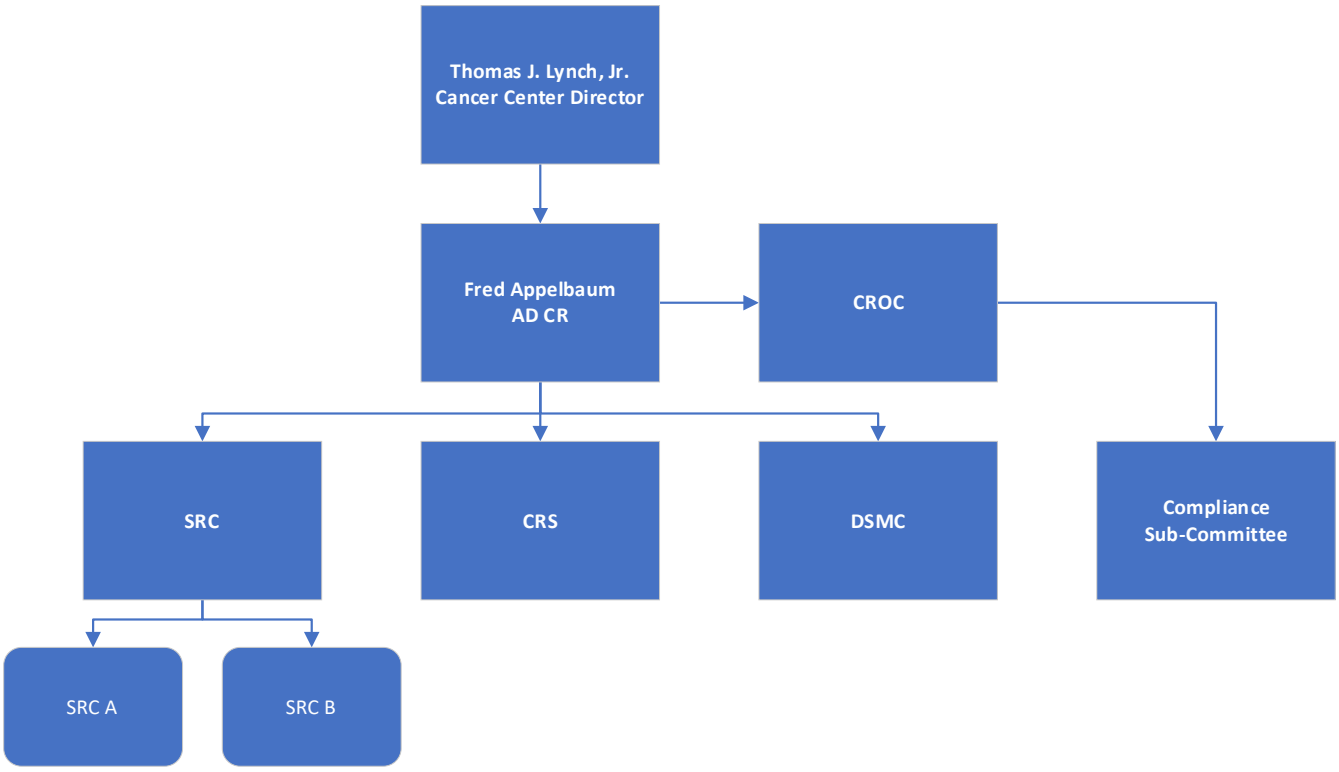
nature of the conflict. The Chair will also inform the committee of the existence of any conflicts that were disclosed to them by members prior to each meeting.

- When a Covered Person on SRC and DSMC has a conflict of interest, they may not participate in the discussion and voting phases of the protocol in question and must leave the meeting for the duration of the review.
- When the Covered Person with a conflict of interest is a SRC or DSMC Chair, another member without a conflict will be appointed to chair the discussion for that review.
- The SRC and DSMC meeting minutes will record the name of any member or Chair with a conflict of interest who is required by guideline to not participate in the discussion and is not permitted to vote.

9.0 APPENDICES

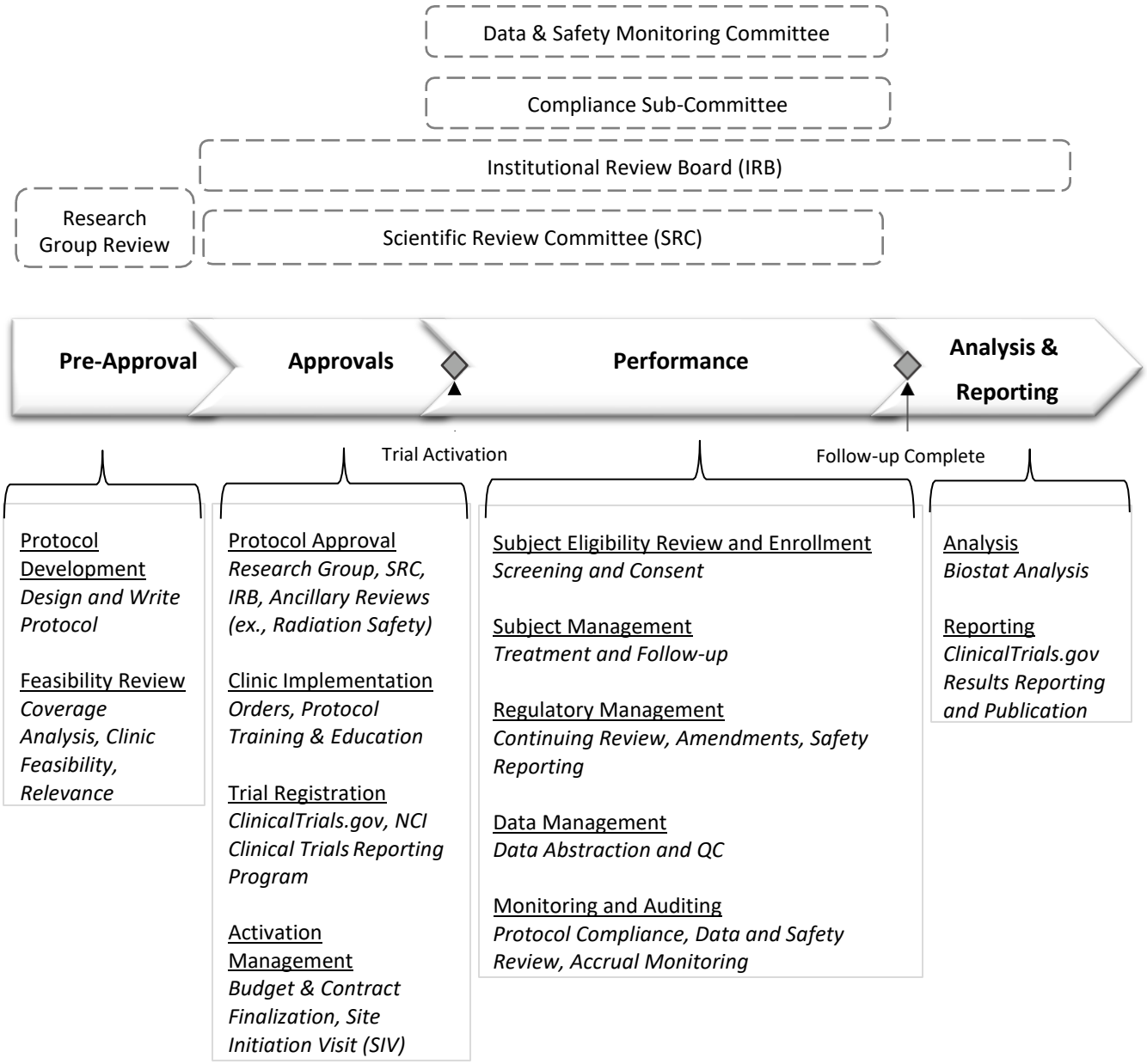
APPENDIX 1: OVERSIGHT COMMITTEES

The Associate Director for Clinical Research (AD CR) reports to the Cancer Center Director and chairs the Clinical Research Oversight Committee (CROC).



APPENDIX 2: CLINICAL TRIAL PROCESS AND REVIEW COMMITTEES

Monitoring occurs throughout the entire clinical trial process from Pre-Approval through Analysis and Reporting.



APPENDIX 3: NIH POLICY WEBSITES

For additional information, refer to the following:

- NIH Policy for Data and Safety Monitoring, NIH Guide 6/10/98 (https://grants.nih.gov/grants/guide/notice-files/not98-084.html)

- Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials, NIH Guide 6/11/99 (https://grants.nih.gov/grants/guide/notice-files/not99-107.html)

- Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials, NIH Guide 6/5/00 (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html)

- Essential Elements of a Data Safety and Monitoring Plan for Clinical Trials Funded by the NCI (https://rrp.cancer.gov/clinicalTrials/data_safety_monitoring_plan.htm)

APPENDIX 4: COMMITTEE ROSTERS

RESEARCH DISEASE & MODALITY GROUPS

The current Research Group membership roster is available on the Cancer Consortium site: https://www.cancerconsortium.org/en/support/study-management/study-start-up/committee-reviews/Research-Group-Review.html

SCIENTIFIC REVIEW COMMITTEE ROSTER

The current SRC membership roster is available on the Cancer Consortium site: https://www.cancerconsortium.org/en/support/study-management/study-start-up/committee-reviews/src.html

DATA AND SAFETY MONITORING COMMITTEE (DSMC) ROSTER

The current DSMC membership roster is available on the Cancer Consortium site: https://www.cancerconsortium.org/en/support/study-management/study-conduct/AnnualRenewal/dsmc.html

COMPLIANCE SUB COMMITTEE ROSTER

Member	Title
Evan Yu, MD	CRS Medical Director
Kristi Stiffler, MPH	Vice President of Clinical Research
Nora Olsen, MS, CCRA	Director of Regulatory Affairs and Compliance