Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Yale Cancer Center
Data and Safety Monitoring Committee
Charter

Version 3.0

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Contents

1 DEFINITIONS

Interventional clinical trials: 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.

Yale Cancer Center Quality and Education unit: The coordinating unit responsible for providing administrative support for Yale Cancer Center's DSMC.

Treatment clinical trials: Protocol designed to evaluate one or more interventions for treating a disease, syndrome, or condition.

2 MISSION

The mission of the Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) is to provide ongoing data and safety monitoring for interventional cancer and cancer-related clinical trials, which includes treatment, interventional prevention and interventional supportive care studies. The Committee reviews serious adverse events (SAEs), protocol-level deviations, subject-level deviations, summary information regarding multi-center investigator-initiated studies led by Yale, and internal and external audit reports at each convened meeting.

3 AUTHORITY

YCC DSMC is an oversight committee, which is an integral component to both the YCC institutional data and safety monitoring plan and protocol-specific data and safety monitoring plan for trials conducted at YCC.
The DSMC has the authority to intervene in the conduct of studies conducted by YCC, as necessary, to ensure the safety of the study participants and to maintain the highest quality in the clinical research performed at YCC. The DSMC may take the following actions during the study which include but are not limited to: require additional monitoring and/ or more frequent reporting on study progress and serious adverse events, require the establishment of a data and safety monitoring board (DSMB), or require the appointment of a medical monitor or an ad hoc safety committee, external to the DSMC.

Trials being monitored by the YCC DSMC will remain under the YCC DSMC purview until a DSMC review has occurred that includes the research activity of the last subject who completed the intervention, or until the DSMC feels there are no subject safety concerns that require further monitoring. The DSMC will determine the length of continued DSMC review on a study-by-study basis.

4 MEMBERSHIP

The DSMC is comprised of voting and non-voting members. There will be a minimum of ten voting members of the DSMC. A minimum of half plus one voting members must be present to satisfy quorum requirements for a meeting. Voting members may include physicians, statisticians, and nurses, based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of clinical trial methodology.

The YCC Director appoints all members of the DSMC and the DSMC Chair. At least bi-annually and whenever membership changes, the YCC Director will perform an assessment of the membership composition. The

assessment considers areas of expertise and committee needs in addition to ongoing members' rates of attendance, participation in meetings, and quantity of reviews performed. For studies requiring special expertise, the DSMC Chair may request the YCC Director appoint ad hoc non-voting members to provide advice on protocols.

A list of current DSMC members is maintained by the YCC Quality and Education unit.

4.1 Chair

The DSMC is chaired by a senior YCC member. The Chair has ultimate responsibility to the YCC Director for meeting CCSG guidelines, including attending at least 80% of meetings. The chair duties include, but are not limited to:

- following up on committee actions.
- ensuring timely execution of correspondence.
- consulting on reviewer assignments.
- completing reviews.
- communicating with Principal Investigators (PIs) regarding DSMC actions, when necessary.
- reviewing meeting agendas.
- acknowledging meeting minutes.
- evaluating member attendance and performance.
- mentoring voting members of the DSMC.
- mentoring and assigning responsibilities to Vice Chair.
- evaluating committee composition.

4.2 Vice Chair

The Vice-Chair is appointed by the YCC Director following recommendation from the Chair. The Vice-Chair plays a pivotal role in assuring timely and consistent quality reviews. Vice-Chair duties include, but are not limited to: completing reviews and mentoring voting members of the DSMC as assigned by the Chair. The Vice-Chair chairs in the absence of the Chair.

4.3 Committee Members

Committee members/voting members of DSMC will represent the following disciplines:

- Medical Oncology
- Radiation Oncology
- Surgical Oncology
- Yale Human Research Protection Program (HRPP)
- Biostatistics
- Ad hoc membership (if special expertise is needed)

Current voting members of the DSMC may be assigned as mentors to incoming voting members.

4.4 Ad Hoc Members

Ad hoc members may be called upon to review studies when specific expertise is required. When an ad hoc member is called upon to review a study, they will serve as a voting member of the DSMC for their ad hoc review.

5 RESPONSIBILITIES

5.1 Committee Members

New members undergo orientation and training with the YCC Quality and Education unit to review DSMC procedures, meeting format, and review instructions.

Members are expected to attend 75% of the meetings held in a calendar year. Decisions regarding recruitment will be made to ensure that membership has the diverse expertise and knowledge required for appropriate review of the research within the scope of the DSMC.

The members of the DSMC will:

1. Gain familiarity with the research protocol(s) and plans for the data and safety monitoring within the scope of their assigned review.
2. Evaluate the data (i.e., protocol-specific data and safety monitoring report, audit report, multi-center activity report, SAE report and/or deviation report) to determine protocol progress and whether the trial should continue as originally planned, should be changed, or should be terminated based on these data.

The YCC Director expects that the DSMC will act in a way that is consistent with the intent of the design of a protocol and in the best interests of the study participants. Based upon evaluation of the data, the DSMC may recommend changes to the design of a protocol because either the assumptions made in the original design are no longer true, or because of data external to the study. The deliberations of the DSMC will not be influenced by special interests of either the study team or a study sponsor.

5.2 Principal Investigator and Clinical Research Team (CRT)

5.2.1 SAEs and Deviations

The Principal Investigator or research team designee will update OnCore on an on-going and timely basis with all unanticipated problems including deviations and SAEs (per the FDA Definition) from the time of each subject's first study intervention through 30 days after the last study intervention, unless otherwise dictated by the IRB-approved protocol.

SAEs, protocol-level deviations, and subject-level deviations recorded in OnCore are reviewed at each convened meeting, or approximately monthly, by an assigned DSMC reviewer. SAEs and deviations are reviewed individually as well as is in aggregate to assess trends. If the DSMC observes toxicities that are unexpected and/ or occurring at greater frequency than previously known or recognized, the DSMC may require additional monitoring and/ or stop the trial due to safety concerns. If a protocol has a disproportionate number of deviations, the DSMC may require a corrective and preventive action plan or additional monitoring.

The Principal Investigator in conjunction with the research team designee in each Clinical Research Team (CRT) is expected to review monitoring reports from external sponsors and collaborators to ensure that all applicable deviations and SAEs identified are entered into OnCore in order to facilitate a comprehensive report of SAEs and deviations for DSMC review.

5.2.2 Two-Stage Design with Stopping Rules

For investigator-initiated trials led by Yale that have a two-stage design with stopping rules, the Principal Investigator will submit a summary of progress to date outlining responses or other criteria used in the protocol to determine moving to the second stage of the trial. Prior to beginning accrual to the second stage, the DSMC will review the summary and data and determine if it's appropriate to continue the study as planned.

5.2.3 Protocol Specific Data and Safety Monitoring Reports

The Principal Investigator or research team designee will prepare a Data and Safety Monitoring Report for each protocol being monitored by the DSMC. This report will summarize the current status of the study, including enrollment and toxicity information, and may also contain information regarding study-related issues for consideration by the DSMC. The report will follow a template which is distributed by Quality and Education committee staff to the research team. The requirements of the report/ materials to be submitted for DSMC review are sponsor-type specific and may include the following:

- Study Narrative written, signed, and dated by PI
- OnCore DSMC Console Export Report
- Most recent annual renewal submitted
- Most recent monitoring report, as applicable
- Most recent external DSMB report/summary from Sponsor, as applicable

The Protocol Review Committee (PRC) is responsible for the initial assignment of a protocol specific data and safety monitoring plan (DSMP). At the time of the initial review, the PRC evaluates the study to determine an adequate protocol-specific DSMP based on trial sponsorship and a quality assurance risk level.

Studies without external monitoring, such as investigator-initiated trials, have a protocol-specific DSMP which typically includes DSMC review every six months. Higher risk studies, regardless of external monitoring, may be assigned for DSMC reviews every six months or more frequently by the PRC.

A risk assessment score sheet [Appendix A] is completed by the YCC Quality and Education unit in conjunction with the YCCI Office of Quality Assurance and Monitoring for every trial reviewed by DSMC. The risk assessment determines the institutional audit schedule as described below.

Risk Assessment Score	Initial Audit
> 10	100% audit of the first 2 subjects accrued, regulatory, pharmacy or device records for study interventions(s)
7- 10	Consent & eligibility audit for first 2 subjects, regulatory
< 7	Random (1 trial per month from pool of low-risk studies with at least two subjects accrued; rotate CRTs): Consent & eligibility for random selection of 2 subjects, regulatory

5.2.4 Audit Reviews

When completing internal audit reviews, the DSMC will set the timeframe for the next internal audit. Typically, investigator-initiated trials and each Smilow Cancer Hospital Care Center are audited annually. The DSMC may adjust the audit schedule based on their review. For external audit reviews, the committee may require a corrective and preventive action plan and/ or additional monitoring, if deemed necessary.

5.2.5 Summary Report for Multi-Center Investigator Initiated Trials

The YCC Quality and Education unit compile a report of summary information related to multi-center IITs led by Yale. The report is compiled using information recorded by the PI and/ or PI designee in OnCore. The report includes the study identifiers, percentage of case report forms which are incomplete, participating institutions, and, for each site, the enrollment status, overall accrual, number of subjects on study intervention, number of SAEs reported, date of the last SAE, number of deviations reported and date of last deviation. Changes from the last report are flagged for the committee to review.

5.3 Yale Cancer Center Quality and Education Unit

The YCC Quality and Education unit coordinates the DSMC meetings. This includes:

- Notifying the research teams regarding the data and safety monitoring review of their studies approximately one month prior to the assigned DSMC review date
- Preparing the agenda and meeting materials
- Sending the meeting materials to the DSMC members at least one week in advance of the meeting
- Tracking attendance
- Preparing the DSMC meeting minutes
- Communicating committee decisions to the investigator in writing
- Maintaining DSMC statistics in the clinical trials management system, OnCore, including DSMC and audit reviews, actions and future review dates.

6 DETERMINATIONS/PROCEDURES

The DSMC may make the following determinations on DSMC reviews for trials with accrual:

- approve a study to continue as planned
- request additional information
- place the study on administrative hold
- terminate a study

The DSMC may request more information or clarification from the PI prior to approving a study to continue as planned. The PI of a study which has unresolved issues is required to submit a response within a timeframe set by the committee, usually allowing for re-review at the next meeting. If a corrective and preventive action plan is necessary, a timeframe for completion will be set and a follow up schedule will be put into place to evaluate the corrective and preventive action plan.

The DSMC may place trials on administrative hold (temporary closure to accrual) for some of, but not limited to, the following reasons:

- Serious unexpected adverse event(s) that significantly alter the risk
- Serious or multiple deficiencies in study conduct (e.g., lack of informed consent, violation of study participant eligibility criteria, failure to report serious adverse event(s), etc.)
- Lack of compliance with federal regulations
- New data suggesting the protocol cannot achieve study objectives, or which significantly alters the risk/benefit ratio
- Multiple major deficiencies in an internal or external audit and/ or monitoring report
- Evidence of serious scientific misconduct or unsafe practices.

The PI is expected to communicate administrative holds of trials applied by the DSMC to the IRB of record as per their written policies and procedures.

For trials that have zero accrual at their scheduled DSMC review, the DSMC will acknowledge the trials by placing them on a dedicated section of the agenda and scheduling a future review date. No protocol specific determination will be made as a review of subject safety, deviations or data did not occur.

7 DSMC Meeting

7.1 Schedule

Meetings are held approximately monthly and on an ad hoc basis, as needed. Meeting may be cancelled with approval from the Chair. The meeting schedule and corresponding submission deadlines can be found on the DSMC website.

7.2 Quorum

A minimum of half plus one voting members must be present to satisfy quorum requirements for a meeting.

7.3 Attendance and Conflicts of Interest

DSMC members will be expected to follow the Yale University guidelines for disclosing conflicts of interest. Committee members who have a COI may be asked to recuse themselves from a protocol discussion and determination deliberations, as appropriate.

7.4 Meeting Conduct

The Chair, Vice Chair or Chair designee, or a member identified, as needed, in times of Chair/Vice Chair recusal or absences, will begin the meeting when quorum is met. The meeting structure includes follow-up on past identified action items, presentation, discussion and determination of internal and external audit reports, review and discussion of the SAE report, review and discussion of the deviation report, review and discussion of multi-center activity report, and review, discussion and determinations of the protocol-specific DSMC reviews. Primary reviewers present a detailed overview of their assigned report(s), members discuss the report, recommendations and required responses from the PI are discussed and consensus reached on appropriateness of response or need for more information.

7.5 Minutes

YCC Quality and Education unit attends DSMC meetings to record minutes, which includes a detailed summary of the meeting discussion and all recommendations for and required responses from the PI. Minutes are provided to the DSMC Meeting Chair or Chair Designee for acknowledgement.

8 ESCALATION

The YCC Director will adjudicate any disagreements between the DSMC and Principal Investigator.

8.1 Appendix A: Risk Assessment Score Sheet

Yale Center for Clinical Investigation

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Protocol Risk Assessment Score Sheet

IRB#: Primary Investigator: Dept/Div:

Risk Factors		Score	Comments
Phase (Select 1 from the group below)			
Phase I	(worth 5 points; add 2 pts if First in Human)		
Phase II	(worth 4 points; add 1 pt for Stopping Rules)		
Phase III	(worth 3 points)		
Phase IV/Expanded Access	(worth 1 point)		
Non-therapeutic	(worth 0 points)		
Phase 0/Feasibility/Pilot/behavioral intervention/ Diagnostic	(worth 3 points)		
Phase Total Points			
Sponsor (Select 1 from the group below)			
Investigator Sponsor (Investigator Initiated Trial (IIT) with an FDA Investigational New Drug (IND) or Investigational Device Exemption (IDE))	(worth 5 points)		
IIT — no IND or IDE	(worth 4 points)		
Government (NIH, NCI, etc.)	(worth 3 points; add 1 pt if no sponsor monitoring)		
Industry	(worth 2 points)		
Subtotal			
Modality			
Number of treatment modalities	(worth 1 point for each modality >1)		
Subtotal			
Agent or Intervention Risk Factors (Select 1 or more from the group below)			
Not Applicable	(worth 0 points)		
>1 invasive procedure	(worth 3 points)		
Device	(worth 3 points)		
Bone Marrow Transplant/Peripheral Blood Stem Cell Transplant/ Gene Therapy/ Gene Transfer studies/ Cellular Manipulation	(worth 4 points)		
Radio-labeled research studies	(worth 4 points)		
Agent developed with Yale input	(worth 4 points)		
Subtotal			
Biospecimens (Select if applicable)			
Not Applicable	(worth 0 points)		
Research Tissue or Blood Samples (Trial with correlative component/ Pharmacokinetics/Pharmacodynamics/ Immunogenicity studies)	(worth 3 points)		
Subtotal			
Expected Accrual Rate (Select if applicable)			
Not Applicable	(worth 0 points)		
Trial to be completed in < 12 months	(worth 4 points)		
High accruing	(worth 3 points)		
Subtotal			
Multi Center — Yale as Lead (Select 1 or more from the group below)			
Not Applicable	(worth 0 points)		
1-3 additional sites	(worth 2 points)		
> 3 sites	(worth 5 points)		
1 or more international sites	(worth 3 points)		
Smilow Hospital Care Centers (SHCC) — off main campus	(worth 2 points)		
Yale-New Haven Hospital (YNHH) affiliates	(worth 2 points)		
Subtotal			
Populations (Select 1 or more from the group below)			
Not Applicable	(worth 0 points)		
Children (teens of child bearing potential code once)	(worth 3 points)		
Prisoners	(worth 3 points)		
Women of child bearing potential (w/ treatment/risks)	(worth 3 points)		
Decisionally Impaired	(worth 3 points)		
Culturally sensitive and/or Certificate of Confidentiality	(worth 3 points)		
Subtotal			
Special Circumstances (Select if applicable)			
Not Applicable	(worth 0 points)		
Yale Institutional Review Board (IRB) is not IRB of record	(worth 3 points)		
First trial for this Principal Investigator	(worth 1 point)		
Subtotal			
Total Score			

Quality Assurance Team Reviewer: Date:

Score >10 = High Risk. 100% audit of first 2 subjects. Depending upon audit findings, committee determines next steps.

Score 7–10 = Moderate Risk. Regulatory, Eligibility & Consent audit for first 2 subjects. Depending upon audit findings committee determines next steps.

Score < 7 = Low Risk, Random Selection. Regulatory, Eligibility & Consent review for randomly selected subjects, rotating through departments. Depending upon audit findings committee determines next steps.

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