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

Yale Cancer Center
Data and Safety Monitoring Committee
Charter

Version 2.0

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

Contents

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.

Office of Quality Assurance and Monitoring (OQAM): Office responsible for providing administrative support to the Yale Cancer Center review committees.

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

Mission

The mission of the Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) is to provide ongoing data and safety monitoring for all interventional cancer clinical trials. The Committee reviews serious adverse events (SAEs), protocol-level deviations, subject-level deviations, internal and external audit reports and a multi-center activity report at each convened meeting. Protocol-specific data and safety monitoring reports are reviewed at a convened meeting at the frequency initially determined by the Protocol Review Committee (PRC) based on trial sponsorship and a quality assurance risk score.

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.

Upon completing a review and discussion of agenda items, the DSMC will decide whether the study should continue as planned, require modification/amendment, or be placed on administrative hold with accrual temporarily closed. The principal investigator is expected to communicate administrative holds of trials applied by the DSMC to the institutional review board (IRB) of record as per their written policies and procedures.

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.

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

Membership

The DSMC is comprised of voting members. The YCC Director appoints all members of the DSMC and the DSMC Chair. There will be a minimum of ten voting members of the DSMC. Membership includes a broad range of representation from the YCC community and including investigators who are engaged daily in clinical research activities, protocol oversight, design and conduct. Voting members may include but are not limited to physicians, statisticians and nurses, based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of clinical trial methodology. 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 Office of Quality Assurance and Monitoring (OQAM). Refer to *YCC Research Oversight Committees Membership Guidelines* for more information regarding recruitment, appointment and terms, evaluation of membership, Ad Hoc members and mentoring.

Chair

The DSMC is chaired by a senior YCC member and is appointed by the YCC Director. 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.
- reviewing and approving meeting minutes.
- evaluating member attendance and performance.
- mentoring voting members of the DSMC.
- mentoring and assigning responsibilities to Vice Chair.
- evaluating committee composition.

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.

Voting Members

Voting members are appointed by the YCC Director. Voting members of DSMC will represent the following disciplines:

- Medical Oncology

- Radiation Oncology or Surgery
- Yale Human Research Protection Program
- Biostatistics
- Ad hoc membership (if special expertise is needed)

Senior voting members of the DSMC may be assigned as mentors to new committee members.

Ad Hoc Members

Ad Hoc members are appointed by the YCC Director. 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.

Responsibilities

Membership

New members undergo orientation and training with the OQAM Regulatory Analyst and/ or the Assistant Director of OQAM to review DSMC procedures, meeting format, and review instructions.

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.

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.

Protocol Review Committee (PRC)

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 in the context of the risk level of the study, the existence of a plan for external monitoring by the sponsor or an independent Data and Safety Monitoring Board (DSMB) or equivalent and other special circumstances that the committee feels will impact the safety of the participants.

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 OQAM for every trial reviewed by PRC. The risk assessment total score guides the timing of the initial audit which is noted on the PRC agenda. The PRC may adjust the audit schedule based on their review. The standard audit schedule is as follows:

Risk Assessment Score	Initial Audit
> 10	100% of the first 2 subjects accrued, regulatory, pharmacy for investigational products
7- 10	Consent & eligibility for first 2 subjects, regulatory
< 7	Random (1 trial per month; rotate YCC Translational Working Groups): Consent & eligibility for 2 subjects, regulatory

Principal Investigator and Research Team

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 thru 30 days after the last study intervention, unless otherwise dictated by the IRB-approved protocol.

The Principal Investigator in conjunction with the research team designee in each Disease Aligned Research Team (DART) 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.

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.

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 OQAM 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

External Audit Reports

The Principal Investigator or research team designee is required to submit external audit reports, not interim monitoring visit reports, within 30 days of receipt to the DSMC for review. This includes Cooperative Group audit reports, industry sponsor audit reports and regulatory agency written observations.

DSMC Recommendations

The Principal Investigator will implement recommendations from the DSMC expeditiously. When requested by the DSMC, the PI will respond in writing to the DSMC outlining the actions taken regarding the recommendations and the rationale for the actions. Responses must be received by the deadline outlined in the committee letter.

Office of Quality Assurance and Monitoring

Office of Quality Assurance and Monitoring staff coordinate 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
- Preparing the meeting room including AV equipment
- Tracking attendance
- Preparing the DSMC meeting minutes
- Communicating committee decisions to the investigator in writing after minutes are approved by the Chair.
- Maintaining DSMC statistics in the clinical trials management system, OnCore, including DSMC and audit reviews, actions and future review dates.

Procedures

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

- Approve
- Approve with recommendations
- Place the study on administrative hold
- Terminate

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.

When completing audit reviews, the DSMC will set the timeframe for the next internal audit. Typically, investigator-initiated trials, each Care Center and cooperative groups are audited annually, but the DSMC may adjust the audit schedule based on their review.

The DSMC may approve a study to continue as planned or request more information or clarification from the investigator prior to approval. PI's of studies with unresolved issues are 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 preventative 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 preventative 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/benefit ratio
- Serious or multiple deficiencies in study conduct (e.g., lack of informed consent, violation of subject 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.

DSMC Meeting

Schedule

Meetings are held approximately monthly and on an ad hoc basis, as needed. Depending on the nature and volume of the trials being monitored, meetings may take place by conference call or be cancelled with approval from the Chair. The meeting schedule can be found on the DSMC website.

Quorum

Quorum for this committee is achieved with meeting attendance from at least half of the voting members.

Attendance and Conflicts of Interest

Members sign in at each committee meeting and declare in writing any conflicts of interest (COI). 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.

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.

Minutes

OQAM staff 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 review and approval post-meeting.

Escalation

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

Appendix A: Risk Assessment Score Sheet

Yale Center for Clinical Investigation

Office of QA and Training
2 Church Street South
Suite 112
New Haven, CT 06519

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.

YCCI Office of Quality Assurance and Training Form Version 5. Date: March 27, 2017.