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

Yale Cancer Center
Data and Safety Monitoring Committee Charter

Purpose/Mission

The purpose 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, which include therapeutic, intervention prevention and intervention supportive care studies. The Committee reviews all SAEs, protocol and subject deviations and internal and external audit reports monthly and protocol specific data and safety monitoring reports at the frequency initially determined by the Protocol Review Committee based on trial sponsorship and risk. The DSMC has authority to intervene in the conduct of these studies as necessary to ensure the safety of the participants and to maintain the highest quality in the clinical research performed at YCC. The 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 for trials conducted at YCC.

This charter describes the authority, responsibilities and membership of the DSMC, and the schedule and structure of its meetings.

Authority

The DSMC will make the following final determinations on all 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 by scheduling a future review, however no protocol specific determination will be made as no review of subject safety, deviations or data can take place.

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 which have unresolved issues are required to submit a response within a given timeframe set by the Committee, usually allowing for re-review at the next meeting. If a corrective action plan is necessary, a timeframe will be set and a follow up schedule will be put into place to evaluate the corrective action plan.

The DSMC has the authority to require additional monitoring or more frequent reporting on study progress and serious adverse events, require the establishment of a DSMB, or require the appointment of a medical monitor or an ad hoc safety committee, external to the DSMC, during the course of the study.

Upon completing the review, the DSMC Committee will approve whether the study should continue as planned, require modification/amendment, or be placed on administrative hold with accrual temporarily closed.

The DSMC may place trials on administrative hold (temporary closure to accrual) for some, 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 patient eligibility criteria, failure to report an adverse event(s), etc.).
- Lack of compliance with IND obligations
- New data suggesting the active protocol cannot achieve study objectives, or significantly altering the risk/benefit ratio
- Multiple major deficiencies in an internal or external audit or monitoring report
- Evidence of serious scientific misconduct or unsafe practices

Administrative holds of trials by the DSMC will be communicated to the Yale IRB in writing. Serious issues concerning safety, compliance, or scientific misconduct are communicated to the YCC Clinical Research Executive Committee. Decisions made by DSMC may be appealed by the PI to the YCC Clinical Research Executive Committee.

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 patient safety concerns that require further monitoring. The DSMC will determine the length of continued DSMC review on a study-by-study basis.

Responsibilities

Protocol Review Committee (PRC):

The Protocol Review Committee (PRC) is responsible for the initial assignment of a protocol specific Data and Safety Monitoring Plan. At the time of the initial review, the PRC evaluates the study to determine an adequate protocol specific Data and Safety Monitoring Plan 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) and other special circumstances that the committee feels will impact on the safety of the participants.

Typically for studies without external monitoring, such as investigator-initiated trials, the protocol specific Data and Safety Monitoring Plan includes DSMC review every six months. Higher risk studies, regardless of external monitoring, may be assigned by the PRC based on their review and evaluation, six month reviews or more frequent reviews.

The PRC will be provided the risk assessment score sheet [Appendix A], completed by the Office of QA and Training, for every trial reviewed. The risk assessment total score guides the timing of the initial audit, however 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 deviations and SAEs per the FDA definition (http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm) from the time of each subject's first intervention thru 30 days after the last intervention, unless the protocol dictates SAE reporting after consent or a longer follow-up period for SAE reporting.

The Principal Investigator in conjunction with the research team designee in each Translational Working Group (TWG) will review monitoring reports from external sponsors to ensure that all applicable deviations and SAEs identified are entered into OnCore in order to facilitate a complete monthly report of SAEs and deviations for the 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 approve continuing 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 recommendations regarding on-study related issues for consideration by the DSMC. The report will follow a template distributed by Office of Quality Assurance and Training staff to the research teams. The requirements of the report/materials to be submitted for DSMC review are sponsor-type specific but 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 upon receipt, not interim monitoring reports, to the DSMC for review. This includes Cooperative Group audit reports, industry sponsor GCP audit reports and FDA 483s observations.

DSMC Recommendations
The Principal Investigator should implement recommendations from the DSMC expeditiously. When requested by the DSMC, the protocol PI will respond in writing to the DSMC of the actions taken regarding the recommendations and the reasons for that decision.

The YCC Clinical Research Executive Committee will adjudicate any disagreements between the DSMC and Principal Investigator.

DSMC Members

The members of the DSMC will:
(1) Familiarize themselves with the research protocol(s) and plans for the data and safety monitoring.
(2) Evaluate the data (i.e. protocol specific data and safety monitoring report, audit report, SAE report and/or deviations report) to determine protocol progress and whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.

Yale Cancer Center 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 should not be influenced by special interests of either the study team or the protocol sponsor.

Each member of the DSMC must sign a confidentiality agreement. DSMC members will be expected to follow the Yale University guidelines for disclosing conflicts of interest. If the member is affiliated with any of the trials under review, he/she will be asked to recuse his/herself for the determination of that trial.

Office of Quality Assurance and Training

Office of Quality Assurance and Training staff coordinates the meetings. This includes:

- Notifying the research teams regarding the data and safety monitoring review of their studies a 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
- Track attendance
- Preparing the DSMC meeting minutes
- Communicating the committee decisions to the investigator in writing within one week of the meeting. This includes determinations and acknowledgements of trials with zero accruals.
- Maintain DSMC statistics in the clinical trials management system, OnCore, including DSMC and audit reviews, actions and future review dates

Membership

The DSMC membership includes both voting and non-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. Voting members may include physicians, statisticians, 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 YCC Chair may request the YCC Director appoint ad hoc non-voting members to provide advice on protocols. The voting members of the DSMC will represent the following disciplines:

- Medical Oncologists
- Radiation Oncologist or Surgeons
- Yale IRB- Chair of Oncology Board
- Statistician
- Ad hoc membership (if special expertise is needed)

With the prospective permission of the DSMC Chair, guests may attend a DSMC meeting to observe for educational purposes. The invited guest will be required to sign a confidentiality agreement prior to the meeting. If the invited guest is affiliated with any of the trials under review, he/she will be asked to leave for the closed session review of that trial.

Meeting Structure

Once a quorum is determined (a minimum of six of the voting members), meetings will take place. Meetings are held monthly and on an ad hoc basis. 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 structure includes the review and approval of past minutes, follow-up on past identified action items, presentation and discussion of internal and external audits, review and discussion of the monthly SAE report, review and discussion of the monthly deviation report and review, discussion and determinations of the protocol specific DSMC reviews.

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Appendix A

Risk Factors	Points	Comments
Phase		
Phase I (add 2 pts First in Human)	5	
Phase II (add 1 pt for Stopping Rules)	4	
Phase III	3	
Phase IV/Expanded Access	1	
Non-therapeutic	0	
Phase 0/Feasibility/Pilot/behavioral intervention	3	
Sponsor		
Investigator Sponsor (IIT - IND)	5	
IIT - no IND	4	
NIH - NCI etc (add 1 pt if no sponsor monitoring)	3	
Industry	2	
Modality		
>1 (add point for each modality)		
Agent or intervention risk factors		
>1 invasive procedure	3	
Device	3	
Bone Marrow Transplant	4	
Gene transfer studies	4	
Radio-labeled research studies	4	
Agent developed with Yale input	4	
Cellular manipulation	3	
Tissue or blood samples		
>10 research samples per subject	3	
Expected Accrual Rate		
Trial to be completed in < 12 months	4	
High accruing (including Expanded Access)	3	
Multi Center - Yale as Lead		
1-3 additional sites	2	
> 3 sites	5	
1 or more international sites	3	
SHCC - off main campus	2	
YNHH affiliates (Greenwich)	2	
Populations		
Children (teens of child bearing potential code once)	3	
Prisoners	3	
Women of child bearing potential (w/ treatment/risks)	3	
Culturally sensitive and/or Cert. of Confidentiality	3	
Special Circumstances		
YU IRB is not IRB of record	3	
First trial for a PI	1	
Total Score		