Data and Safety Monitoring Plan

Leonidas C. Platanias, MD, PhD, Director
The Robert H. Lurie Comprehensive Cancer Center
of Northwestern University
303 E. Superior
Chicago, IL 60611
(p) 312-908-5250
(f) 312-908-1372

TABLE OF CONTENTS

Revision History

Initial Approvals:

Revision # & Date	Submission Date	NCI Approval Date
Initial Submission	07/20/2001	08/28/2001
1 – 05/31/2002, 09/2002	09/16/2002	10/2002

Revisions:

Revision #	Revision Date	NCI Submission Date
2	05/24/2005	06/2005
3	05/15/2006	06/2006
4	05/20/2008	06/2008
5	04/23/2009	05/2009
6	4/9/2010	05/2010
7	4/18/2011	05/2011
8	06/30/2011	06/2011
9	10/28/2011	10/2011
10	04/24/2012	05/2012
11	09/14/2012	09/2012
12	05/02/2014	05/2014
13	03/16/2015	05/2015
14	02/02/2016	05/2016
15	05/23/2019	06/2019
16	05/31/2022	06/2022
17	05/31/2024	06/2024

Abbreviations

AER	Adverse Event Report
CAPA	Corrective and Preventative Action Plan
CFR	Code of Federal Regulations
COI	Conflict of Interest
CTAC	Clinical Trial Audit Committee
CTEP	Cancer Therapy Evaluation Program
CTEP AERS	CTEP Adverse Event Reporting System
CTO	Lurie Cancer Center Clinical Trials Office
DCTD	Division of Cancer Treatment and Diagnosis
DCP	Division of Cancer Prevention
DT	Disease Team
DLT	Dose-limiting Toxicity
DSMC	Data and Safety Monitoring Committee
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FSM	Feinberg School of Medicine
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IIT	Investigator-Initiated Trial
IND	Investigational New Drug
IRB	Institutional Review Board
JBVAMC	Jesse Brown VA Medical Center
LCC IIT	Lurie Cancer Center Investigator-Initiated Trial
LCH	Ann & Robert H. Lurie Children's Hospital of Chicago
LOI	Letter of Intent
NCI	National Cancer Institute
NIH	National Institutes of Health
NOTIS	Northwestern Oncology Trial Information System
NU	Northwestern University
PI	Principal Investigator
QA	Quality Assurance
QAM	Quality Assurance Monitor
RNI	Reportable New Information
ROC	Research Oversight Committee
ROS	Research Oversight System
SAE	Serious Adverse Event
SDV	Source Data Verification
SFI	Significant Financial Interests
SIM	Study Implementation Meeting
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
SRAL	Shirley Ryan Ability Lab
SRC	Scientific Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
VAERS	Vaccine Adverse Events Reporting System

* Please note: through this document, all references to online documents can be found on the Lurie Cancer Center website at https://www.cancer.northwestern.edu/research/clinical-trials-office/research-oversight.html

Data and Safety Monitoring Plan

1.0 INTRODUCTION

The Robert H. Lurie Comprehensive Cancer Center (Lurie Cancer Center) of Northwestern University (NU) has a diverse research program, including a large portfolio of protocols in the areas of primary cancer treatment and prevention, cancer control and other interventional trials, observational and outcomes studies, and lab-based research including correlative and ancillary studies. Therapeutic trials range from Early Phase I to multi-institutional randomized Phase III studies. The Lurie Cancer Center is dedicated to ensuring that all clinical trials are appropriately monitored to ensure research participant safety and that the validity and integrity of clinical trial data are maintained. Responsibility for this mission falls to the committees that comprise our Research Oversight System (ROS).

The Lurie Cancer Center's Data and Safety Monitoring Plan (DSMP) has been developed to provide oversight for data and safety monitoring for clinical trials consistent with the following: the *NIH Policy for Data and Safety Monitoring* as of June 10, 1998; *Policy of the NCI for Data and Safety Monitoring of Clinical Trials* as of June 22, 1999; *Further Guidelines on a Data and Safety Monitoring Plan for Phase I and II Trials* from the NIH on June 5, 2000; *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the NCI* as of April 2001; and The Cancer Centers Branch of the National Cancer Institute Parts I and II: Policies and Guidelines Relating to the Cancer Center Support Grant, dated September 2004. This document provides a description of the Lurie Cancer Center's policies and procedures related to data and safety monitoring activities at the center.

2.0 BACKGROUND

2.1 Definition of a Clinical Trial

This plan follows the NIH definition of a clinical trial, released October 23, 2014 that states a clinical trial is "A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes." Interventions may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a present diagnosis of cancer, but who are considered cured from a prior cancer and/or people who are considered to be at risk for developing it in the future.

Diagnostic research utilizing molecular or imaging diagnostics is considered to be a clinical trial if the information from the diagnostic test is used in a manner that affects medical decision-making for the study participant. As such, the information from the diagnostic test may have an impact on some aspect of outcome, and assessment of this impact may be a key goal of the trial. Studies that do not use information from the diagnostic test in a manner that can affect the outcome of study participants, but whose objective is solely the gathering of data on the characteristics of a new diagnostic approach, are not clinical trials and are not covered by this policy (unless performing the diagnostic test itself imposes some risk on study participants).

Behavioral clinical trials include interventions whose goals are to increase behaviors (e.g., cancer screening, physical activity, etc.), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life and reduce the morbidity associated with treatment. Interventions may pertain to cancer prevention, early detection, treatment, and survivorship. Observational studies and those that do not test interventions are not considered clinical trials.

2.2 Applicability

This plan applies to investigators conducting cancer-relevant clinical research within Northwestern

University, Northwestern Medicine, the Shirley Ryan Ability Lab (SRAL, formerly the Rehabilitation Institute of Chicago), the Jesse Brown VA Medical Center (JBVAMC), Ann & Robert H. Lurie Children's Hospital of Chicago (LCH), and at sites participating in Lurie Cancer Center investigator-initiated trials (LCC IITs).

For purposes of this plan, a LCC IIT is a trial authored by a Lurie Cancer Center member or by any NU faculty member conducting cancer-relevant research. LCC IITs covered by this plan include studies supported through various funding mechanisms, including competitive NCI/NIH grants, other agency/sponsor grants or gifts, and grant-in-aid support from pharmaceutical sponsors. These trials are required to comply with the minimum requirements as described in this DSMP, or to develop an alternate plan that must be reviewed and approved by the Lurie Cancer Center's Scientific Review Committee (SRC). Multi-center trials originating at an outside institution are reviewed at SRC submission for adequate data and safety monitoring plans. If the originating site does not have a plan or if the protocol specifies the use of local DSMP oversight, they will be required to comply with the plan outlined in this document for the Lurie Cancer Center to be a participating site. As required by the NCI, other grants and contracts from NCI/NIH (e.g., National Clinical Trial Network studies) and studies developed and funded by industry are excluded from this plan.

2.3 Conflict of Interest

Conflict of Interest (COI) can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement and 45 CFR Part 94. NU has the following COI policies: "Policy on Conflict of Interest and Conflict of Commitment", "Conflict of Interest in Research", and "Institutional Conflict of Interest in Research". These documents outline rules and reporting requirements governing all types of conflicts, including financial conflicts and disclosures, and also outlines policy specifically related to clinical research. Importantly, the NU policy requires that an investigator disclose if the value of any remuneration received from the entity in the twelve months preceding the disclosure and, in the case of publicly traded entities, the value of any equity interest in the entity as of the date of disclosure, when aggregated for the Investigator and members of his or her immediate family, exceeds $5,000. NU employs an online, electronic system for reporting COI, and faculty and staff must report all significant financial interests (SFI) prior to engaging in research and at least annually thereafter; any new SFIs must also be reported within 30 days. These are reviewed by NU COI office and may be referred to the faculty member's respective school and/or the COI Oversight Committee if additional review is required. If any COIs exist, the Dean's office of the respective school and NU COI office will work with NU personnel to develop a plan to manage, reduce or eliminate the COI.

In addition to this University-wide policy, the NU Feinberg School of Medicine (FSM) has adopted a complementary policy titled "Disclosure and Professional Integrity Policy" developed with the integrity of medical research in mind. This policy also requires faculty to report financial COI, but there is no de minimis threshold for disclosure. Instead, all outside professional activities related to the health care industry are to be reported, no matter the payment amounts, and these are posted on the FSM website. Both the NU and FSM policies may be found online at NU COI Policies.

Lurie Children's has a "Financial Conflicts of Interest in Research and Sponsored Programs" policy that is applicable throughout the Lurie Children's organization and requires disclosure of significant financial interest annually, using an online reporting system. Per their policy, significant financial interest in a publicly or non-publicly traded entity exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure, when aggregated, exceeds $5,000. This policy is located online at Lurie Children's COI Policy.

The Lurie Cancer Center abides by all applicable Lurie Children's, NU and FSM COI policies. Any faculty member invited to serve on or to review items for any of the committees described in this DSMP

must disclose any potential COI relevant to committee membership, whether real or perceived, to the appropriate Lurie Cancer Center officials (i.e., the Lurie Cancer Center Director or Deputy Director and/or applicable committee Chair). Potential conflicts that develop during a member's tenure on a committee must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest, or the appearance of conflicts of interest, may participate on a committee or in a particular meeting will be made by the committee chair and/or co-chair and brought to the Lurie Cancer Center Research Oversight Committee (ROC) for documentation purposes.

While the Lurie Children's and NU policies outline general rules related to COI, the Lurie Cancer Center has established the following specific committee rules that govern the activity of members who have a conflict:

- A committee member may not vote on any protocol-specific agenda items pertaining to trials on which he or she serves as a Principal Investigator (PI) or sub-investigator. When a faculty member is present at an SRC meeting and a protocol on which he or she will be a PI or sub-I is being discussed in consideration for initial approval, he or she is required to abstain from voting and placed in a waiting room during review and voting. Investigators may not serve as an auditor for trials on which he or she are the PI or a sub-I.

- Any committee member who is not an investigator on a trial, but who has another identified conflict may or may not be allowed to vote on actions related to the protocol atthe discretion of the committee Chair(s).

2.4 Confidentiality

All discussions that occur within any of the LCC research oversight committees are confidential and are not disclosed except as outlined in this plan. Committee decisions are conveyed to the respective PI and other components of the LCC ROS as required, on behalf of the entire committee via the administrative staff coordinating the meetings, but no specifics are given related to the persons involved or details of the discussion that occurred. Any paper materials containing confidential information distributed during committee meetings are collected and destroyed after each meeting, and access to electronic materials is limited to panel members only.

Further, the committees are especially aware of issues related to confidentiality of data. The committees abide by, and enforce, the design of each study; confidentiality of the data are maintained when data are presented (e.g., treatment assignment is not disclosed). Blinded studies remain so until they are to be un-blinded as per study design, or in response to a safety issue that requires knowledge of treatment received by a study participant.

3.0 INSTITUTIONAL CLINICAL TRIAL RISK ASSESSMENT AND MONITORING REQUIREMENTS

The Lurie Cancer Center expects that all LCC IITs that meet the definition of a clinical trial will follow the data safety monitoring procedures and requirements outlined in this plan. This plan also applies to other (non-LCC IIT) clinical trials that do not have an acceptable external or alternate plan.

3.1 Definitions of Levels of Risk and Associated Monitoring Requirements

The Lurie Cancer Center complies with federal regulations and guidelines, as well as the Lurie Children's and NU IRB Office policies and procedures related to the assignment of trial risk. The "Northwestern Human Subject Protection Policy Manual" is found online at NU IRB Policies. The Lurie Children's "IRB Policy and Procedures Manual" is found at Lurie Children's IRB Policies.

The SRC defines three levels of risk for clinical trials, ranging from minimal to high risk, and takes into account type of intervention, primary purpose, phase/study design, risks to participants, and risks to the institution (i.e. need for IND or IDE). The sample size, proposed study sites, expected duration and

complexity of a trial may also be considered. In the event that a study may be reasonably assigned to two categories, the highest risk category will be selected. Significant changes to the research during the conduct of the study may impact the risk level designation. The level of monitoring and source data verification (SDV) required will correspond with the level of risk assigned and other factors. There may be full SDV required for all data points or partial SDV of some components (such as consent, eligibility/registration, and serious adverse events, etc). A final risk level and corresponding requirements are given in the final SRC outcome letter.

Level of Risk	**Definition**
Minimal Risk	The probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests and where confidentiality is adequately protected. An example of this type of trial is a computer internet-based strategy aimed at increasing awareness of cancer issues, a dietary intervention, or exercise study aimed at symptom management. Monitoring by the Data and Safety Monitoring Committee (DSMC) is not required.
Moderate Risk	There is a probability of a moderate-severity event occurring but there is adequate safety monitoring in the trial to identify events promptly and to minimize their effects. An example of this type of trial is a topical agent used to control a drug rash.
High Risk	There is a high probability of the occurrence of a serious adverse event and/or study monitoring and reporting requirements of the trial are such that events or event trends may not be immediately recognized. **AND/OR** The NU or LCC investigator holds the IND/IDE. An example of this type of trial is a chemotherapy trial aimed at treating cancer.

In addition, the following monitoring guidelines are used to determine the intensity and type of monitoring that is required for the study.

Risk Level	**Primary Purpose is Treatment***	**Trial Phase****	**IND/IDE held by LCC PI**	**SDV**
Minimal	No	Any	No	SDV Not Required
Moderate	No	Any	No	SDV Not Required
Moderate	No	Any	Yes	Partial SDV
Moderate	Yes	Any	No	Partial SDV
Moderate	Yes	Any	Yes	Partial SDV
High	Yes	I	Yes	100% SDV
High	Yes	I	No	100% SDV
High	Yes	II or III	Yes	Partial SDV
High	Yes	II or III	No	Partial SDV
EA/SPIND***	Yes	N/A	Yes	Partial SDV

*Treatment refers to treatment of a cancer (not of a side effect or a supportive therapy)

**Phase I/II trials follow requirements for ph I and then ph II accordingly

***EA = expanded access; SPIND = single patient IND/compassionate use protocol

3.2 Data and Safety Monitoring Boards

In instances in which the funding source and/or the NU or LCH COI management plans requires it, a trial may form an independent Data and Safety Monitoring Board (DSMB). For moderate and/or high risk clinical trials, composition of this board must be proposed by the study PI and approved by the SRC. SRC may also determine in the course of their review that a specific trial requires an independent DSMB and will make this a condition of final approval.Clinical trials that are deemed minimal risk may require the establishment of an independent DSMB. These DSMBs are not required to report under this DSMP, but their composition may be approved by the SRC if required by the funding source or COI management plan.

Appendix D outlines DSMB requirements for medical and non-medical intervention studies.

4.0 RESEARCH OVERSIGHT SYSTEM ORGANIZATION AND ADMINISTRATION

The Lurie Cancer Center has developed a comprehensive system of research oversight, comprised of distinct committees that work collaboratively to provide robust oversight of all aspects of clinical research conducted at the Lurie Cancer Center. The Scientific Review Committee (SRC) and the Disease Teams (DTs) comprise the Center's Protocol Review and Monitoring System (PRMS). The Data and Safety Monitoring Committee (DSMC) includes an Audit Sub-Committeeand is responsible for comprehensive data and safety monitoring as well as protocol compliance. The committees are independent and SRC and DSMC report directly to the Lurie Cancer Center Deputy Director, while the DT leaders report directly to the Associate Director for Clinical Research. The Deputy Director and Associate Director, in turn, reports to the Director of the Cancer Center. The Research Oversight Committee **(ROC)** meets monthly and is comprised of the faculty chairs of SRC and DSMC, as well as the CTO Medical Director, the LCC Deputy Director, the AD for Clinical Research, and senior LCC administrative leaders. A diagram of this system can be found in Appendix A. Committee responsibilities related to data safety monitoring are described below.

4.1 Disease Teams

The primary objective of each DT is to guide in the selection and prioritization of high-quality cancer research studies while taking into account their current DT portfolio and patient population. Each DT includes 2-3 leaders who are responsible for proper functioning of the multidisciplinary team. A listing of DTs and their associated leaders may be found online at Disease Team listing.

The DTs meet at least monthly to review all studies under the purview of their team. DTs serve as the first stage of review and must endorse each newly proposed study before the protocol may be submitted to the SRC. In addition, to providing this first stage of review, DTs may provide input and are used as a resource for the development of LCC IITs); the first level of review may be started at the concept or letter of intent (LOI) stage prior to full protocol development. Both SRC and DSMC communicate with the DT leaders and each other, as needed to inform about any issues or concerns that impact the DT's research portfolio or the safety or scientific integrity of any specific protocol. This includes when the SRC sub-committee sends portfolio review letters to the DT at least annually; in addition, DSMC will send semi-annual reports for moderate and high risk studies and also distributes audit reports as applicable to the DTs.

4.2 Scientific Review Committee (SRC)

The SRC is multidisciplinary committee charged with the responsibility of evaluating new and enrolling clinical research protocols for scientific merit, institutional priority and ongoing progress, including review of accrual and DT portfolios for all clinical trials. The SRC is an independent committee within the Lurie Cancer Center's PRMS, chaired by Al B. Benson III, M.D. and co-chaired by both Masha Kocherginsky, Ph.D. and Priya Kumthekar, MD. A full member listing is included online at SRC membership.

The SRC acts as the second stage review and is primarily focused on the scientific design and importance of new studies, as well as ensuring appropriate data and safety monitoring plans; SRC will not approve protocols that do not include an adequate DSMP. SRC review of LCC IITs includes assignment of risk level as outlined in Section 3.1During ongoing progress review, SRC will notify the DSMC regarding any decisions that impact protocol status (e.g., suspension or closure) or any accrual determinations or recommendations for those studies under DSMC purview.

The DSMC is responsible for informing the SRC of any findings that may impact the safety, progress, or scientific integrity of a trial (e.g., multiple missed data points required for primary endpoint). In the event that the committee is notified of significant misconduct or serious non-compliance (or other issues impacting study integrity), the SRC will help ensure that all appropriate authorities are notified as needed (e.g., the IRB, FDA, NCI, funding sponsor, etc.) according to institutional policies. In the event that a suspension or closure occurs on an NCI funded IIT, the SRC will ensure the PI reports to this the NCI Program Director. The LCC Deputy Director is made aware of all closures as part of the SRC portfolio review meetings.

4.3 Data and Safety Monitoring Committee (DSMC)

The DSMC is an independent committee responsible for the in data and safety monitoring of all LCC IITs and other clinical trials utilizing this DSMP as described above. This is a multidisciplinary committee that consists of a core group of individuals providing the necessary expertise in the principal disciplines of clinical hematology/oncology, radiation and/or surgical oncology, pharmacy, and biostatistics. Members are selected by area of expertise to form a diversified group of clinicians and other professionals able to provide rigorous monitoring of studies. David Vanderweele, MD serves as chair of the committee and Sonali Chaudhury, MD as the co-chair. A full member listing is found online at DSMC membership.

The Deputy Director of the Lurie Cancer Center provides oversight of the administration of the committee as a liaison with the AD for Clinical Research. The Lurie Cancer Center's Quality Assurance (QA) team provides administrative support for the committee, and each study monitor is responsible for reporting trials they monitor at the DSMC meetings. DSMC's review specifically focuses on participant safety and toxicity, outcomes/response, accrual updates, compliance issues, and overall data integrity (see Section 5.1 for information related to monitoring activities).

While the DSMC is a distinct independent committee, DSMC shares its findings with the other committees of the Research Oversight System, as needed, includingnotifying the SRC of any issues they believe to be potentially relevant to the scientific progress or integrity of the trial. The DSMC also communicates with the DTs, informing them of any concerns and providing semi-annual reports (SARs) as necessary for relevant LCC IITs.

The DSMC meets monthly and provides the following:

- Ongoing Study Monitoring: DSMC reviews the progress of all clinical trials monitored by the committee through review of semi-annual reports. The semi-annual reports include summary information for and any recommendations on accrual, adverse events, and compliance issues. These are completed collaboratively by the PI and assigned QAM. Studies not directly monitored by the NU QAM team will follow protocol-specific procedures. These reports will continue until trial is closed to further enrollment, all patients are off study intervention, and no new enrollment, safety, or compliance information is expected. If the DSMC has a recommendation regarding accrual, safety and toxicity, compliance or data compliance, SRC and the associated DT will be notified of the recommendation.

- FDA Report review: DSMC is responsible for the review and release of all FDA annual reports prior to submission to the FDA for those studies where the LCC PI holds the IND or IDE.

- Safety review: DSMC conducts ongoing safety reviews of all clinical trials monitored by the

committee. Safety review includes all serious adverse events and UPIRSOs, as specified in each protocol, that occur on the trial. Any change in SAE term, grade, or relationship to study agent will require re-review. All SAEs are also included in aggregate for review by DSMC as part of the semi-annual report. The DSMC has the authority to suspend or close any study if serious safety concerns are identified and may request further review of all AEs if needed to assess trends.

- Dose Limiting Toxicity (DLT)/Dose Escalation review: DSMC, in conjunction with the study assigned statistician, reviews all potential DLTs for dose-escalation studies. Protocol suspensions and re-opening of accrual to the next cohort, based on DLT evaluation, fall under the purview of DSMC.

- Stopping Rule review: DSMC, in conjunction with the study assigned statistician, will assess safety data and critical efficacy endpoints at intervals defined by the protocol and recommend whether to continue, modify, or stop a trial.

- Protocol Deviation review: All protocol deviations will undergo an initial review by a member of the QA team. Those determined to be potentially reportable to the IRB or represent continued noncompliance will also be reviewed by the DSMC at the next panel meeting. If the DSMC determines a deviation is reportable to the IRB, the QAM communicates this information to the study team; deviations already determined by the study team and/or PI to meet reporting criteria to the IRB will be reviewed along with the CAPA at the next panel meeting. All protocol deviations, including those not initially taken to a panel meeting, are reviewed in aggregate by the DSMC as part of the SAR. The DSMC further has the authority to suspend or close the trial in the event that major protocol compliance issues are found and will notify SRC of such action.

- Reportable New Information (RNIs): All RNIs (as defined by the IRB of record) not already reviewed as SAE/UPIRSOs or reportable deviations but that impact safety or data integrity will will be reported to the DSMC at the next panel meeting.
- Data Set review: Data requests to be used for abstract and/or manuscript development must be reviewed and approved by the DSMC prior to release to the study PI and/or biostatistician. Data will be released in accordance with the Data Release policy.
- Audit Report review: DSMC reviews final audit reports and corresponding corrective and preventative action plans (CAPAs) for all LCC IITs. The DSMC has the authority to require further corrective action, recommend changes to the monitoring plan type or frequency or issue additional audits by the Audit Sub-Committee as needed. The DSMC further has the authority to suspend or recommend closure of a trial in the event that major concerns are found during an audit and will promptly notify the SRC which has ultimate/final authority to close any LCC clinical trials..

4.4 Clinical Trial Audit Sub-Committee (ASC)

The ASC is responsible for coordinating and overseeing the conduct of the LCC's auditing program under the oversight of the full DSMC. A sub-set of DSMC members providing expertise in clinical oncology and research compliance are delegated to ASC tasks and form a diversified group of professionals able to provide rigorous oversight of auditing activities..

The LCC Compliance Operations Team (staffed administratively within the CTO) provides administrative support including assembling an independent audit team for each audit; audit teams may include faculty members, fellows, nursing staff, members of the QA team, and other senior CTO staff. To avoid COI, the faculty and staff cannot be chosen to audit a trial for which they are listed on the IRB's authorized personnel list or for which they are the assigned QAM. The Compliance Team also facilitates audit scheduling, case distribution and assignments, initial compilation ofaudit findings, collection of responses and proposed CAPAs, and coordination of the ASC meetings.

Although each audit team functions independently with staff oversight, allaudits of LCC IITs are reported to the DSMC for final approval and acknowledgment or additional actions which may include::

- Immediate/temporary suspension to accrual and/or further recommending closure of the trial to the SRC
- Termination for a site due to substandard performance; and
- Recommending changes to policy, protocols, or procedures based on cumulative audit findings.

The ASC meets as needed based on the current volume of required/routine and/or for-cause audits .

- Audit scheduling and conduct: Compliance Team staff schedule the audits, assigns auditors, and ensures audits are conducted as required following the NCI's Clinical Trials Monitoring Branch Auditing Guidelines.
- Review of audit findings: ASC reviews all audit findings and makes the final determination on the categories of seriousness for issues identified during the audit. Individual findings are categorized as "lesser" or "major", following NCI CTEP definitions, and determines if the study team must submit a Corrective and Preventative Action Plan (CAPA). All final audit reports including final CAPAs are then presented to DSMC along with any additional recommendations for approval as described above.

Audits are typically focused on trials assessed as high-risk (although moderate and minimal risk trials may undergo for cause or periodic audits if appropriate) and will be audited according to the following plans:

- Comprehensive (Routine) Audits – At least one case, or 10% of participant case accrued since the last audit, will be audited. A representative sampling should be chosen for audit. These are comprehensive audits that include, as applicable to the trial, a review of:
    - Regulatory Documentation, including IRB, Informed Consent Content, Delegation of Authority
    - Accountability of Investigational Agents and Pharmacy Operations
    - Patient Case Records, including informed consent, eligibility, treatment, evaluation of disease outcome/tumor response, reporting of adverse events, and general data quality
- First Participant (Routine) Audits – The first participant to enroll on a trial at the lead institution and the first participant enrolled on a trial at each collaborating site, if applicable, will be audited. The case audit occurs after the first participant has completed the first response assessment or goes off active intervention, whichever comes first. These audits may count towards the comprehensive audit as applicable. These audits include patient case review only unless otherwise requested.
- For-Cause Audits – Trials at risk of or suspected to demonstrate serious or on-going non-compliancemay be undergo additional directed audits; this may be at the request of any component of the ROS. These audits may occur at any time and advanced notice is not required. These audits may consist of a limited or comprehensive review of one or more of the components listed above.

4.5 Lurie Cancer Center Research Oversight Committees and the IRB

NU and Lurie Children's each have independent IRBs but also have a signed Authorization Agreement that allows collaboration for the review of studies impacting both institutions. The SRAL is contracted to use the NU IRB. NU IRB provides six IRB panels, including five that meet monthly and one that meets

weekly (for continuing reviews and other time-sensitive submissions). The Lurie Children's IRB Office provides support for two panels that meet bi-monthly. NU faculty may also use a central IRB for certain types of studies. The Jesse Brown VA Medical Center has an independent IRB that meets twice a month. All new cancer-relevant protocols and revisions must receive the appropriate SRC, IRB, and other required institutional approvals prior to activation or implementation.

The SRC and IRB perform separate but complementary activities, which do not overlap or duplicate effort. The Lurie Cancer Center oversight committees are responsible for scientific review, monitoring, and evaluation of trials for ongoing progress, data and safety monitoring, and auditing. The IRB is responsible for the overall ethical and safety considerations of clinical research with respect to protecting the rights and welfare of human subjects involved in research. Additionally, the IRB ensures that all consent forms adequately express the risks, benefits, alternatives, and financial costs of clinical research protocols. The IRB further ensures HIPAA regulations are followed. Appendix B provides a comprehensive diagram of the relationships among these committees and with the Institutional Review Board (IRB).

QUALITY ASSURANCE MONITORING

The Lurie Cancer Center has made it a priority to continuously strengthen our internal QA program, which reports administratively within the CTO's Compliance Operations Team and carries out the monitoring of all LCC IITs according to risk level and the guidelines described above..

5.0 Quality Assurance Review

The QAMs are responsible for the ongoing review of all clinical trial data for LCC IITs, concentrating on data accuracy and completeness, protocol adherence, and safety review. This includes the review of studies that are supported by competitive federal funding mechanisms that do not have an alternate data management plan.

The QAMs review study conduct and data submitted for trials at scheduled monitoring visits, according to the monitoring plan associated with the study's risk level, and they interact directly with each study PI and team as issues arise. They also work directly with study teams at all participating participating sitesThe QAMs regularly report on study progress, safety, and compliance concerns to the DSMC during monthly meetings and via email, when needed.

The QAMs are intimately involved in data capture and review from protocol implementation through trial completion. Trials opened prior to July 2009 use paper-based case report forms, created by the QAMs. All LCC IITs assessed as moderate or high-risk and opened to accrual after July 2009 use electronic case report forms (eCRFs), built into NOTIS, the Lurie Cancer Center's clinical trial management system. The study assigned QAM builds eCRFs for each new trial in conjunction with the study PI, biostatistician, study coordinator, data manager and/or other study team members to ensure adequate capture of data for all study objectives, eligibility and registration requirements, treatment/intervention, adverse events, and other protocol-driven data
The intensity of monitoring activities varies by the study assigned risk. Based on the outcome of any monitoring activities, additional monitoring parameters may be recommended by DSMC. An overview of the monitoring requirements for moderate and high risk trials is indicated in the table in Section 3.1 and further details are described in the LCC QA Monitoring Guidelines

5.1 Other Quality Assurance Activities for LCC IITs

The QAMs work closely with faculty and staff throughout the life cycle of each protocol, from helping review during initial protocol development through final data analysis and study termination. In addition to providing input during protocol development to PIs and the protocol writing team within the CTO,QA team members serve as assignedreviewers for LCC IITs at SRC and help ensure the trial is assigned an

appropriate risk level. The QAMs also work with the PI and study team to develop eCRFs for the study, help train teams on data entry and participate in the SIVs, perform routine monitoring, serve as audit team members, and also prepare all data for DSMC for review and approval prior to releasing for publication as described in DSMC Data Release Policies and Processes that was developed with our Quantitative Data Sciences Core. Senior members of the QA staff also report results in clinicaltrials.gov and submit all annual and final reports to the FDA as required.

5.2 Adverse Event Reporting Requirements

Adverse event reporting requirements and timing of reporting are dependent on the phase of the trial, the procedures outlined in each protocol, and the the grade and attribution of the event and is completed as outlined in the guidelines published in the NCI Investigator Handbook (http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm). It is the responsibility of the study PI, the treating physician, and clinical team to identify events as they occur. Federal guidelines require timely reporting of all unanticipated adverse events as outlined by the study sponsor.

All Serious Adverse Events (SAEs) must be reported as required by institutional policy and federal guidelines. In addition, adverse events which do not meet the definition of a SAE may also require expedited reporting dependent upon the grade of adverse event, attribution, and whether the event is expected or unexpected. Expedited reporting may not be required for protocols when the adverse event is expected. Any exceptions will be outlined in the text of the protocol. In the event that a participant experiences an event requiring expedited reporting, the report must be submitted to the QA team and to other entities as described in the protocol (i.e. the IRB of record, funding source, etc) using appropriate reporting forms.

21 CFR 312.32, defines a SAE as an adverse drug experience that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours);
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly or birth defect;
- Important Medical Events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Whenever a serious adverse event occurs on an LCC IIT, either at the Lurie Cancer Center or a participating site, the event is submitted to the QAM and is reviewed by the DSMC. The DSMC will review the event and the PI's assessment. For events occurring at a participating site, the lead site PI will also review the event and local PI's assessment. The DSMC may determine the event requires expedited reporting, and in this case, the QAM will follow-up with the PI to help ensure the event is reported to the IRB of record. If an event is determined to require expedited reporting to the IRB, it will also be sent to participating sites as a Suspected Unexpected Serious Adverse Reaction (SUSAR) report requiring IRB submission and consent and/or protocol modification will be sent to the sites as appropriate. See Appendix C for flow diagrams outlining procedures for handling of both internal and external adverse events.

The CTO regulatory team is responsible for processing external SUSARs and ensuring these are reviewed by PIs who hold an IND/IDE for that drug or device. The QAMs then present any SUSARs that the sponsor-investigator determines to qualify as RNIs to the DSMC. Any event determined by the DSMC to be a UPIRSO is routed to participating sites for local IRB submission and consent and/or protocol modification will be sent to the sites as appropriate.

For all NCI funded or sponsored clinical trials, investigators are required to submit events through the CTEP Adverse Event Reports System (CTEP AERS) as described in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" found at https://ctep.cancer.gov/protocoldevelopment/adverse_effects.htm.

If NCI does not hold the IND, the FDA regulations apply as outlined in 21 CFR Part 312.32

(http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32).

If the trial uses commercially available agents/devices SAEs are reported using a format as indicated in the trial or are reported through MedWatch (http://www.fda.gov/).

If the trial involves recombinant or synthetic nucleic acid molecules, the reporting requirements described above must be followed. In addition, the "NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)" apply. This guideline may be found at http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines.

If the trial is a post-marketing vaccine trial, the reporting requirements described above must be followed. In addition, adverse events may be submitted through the Vaccine Adverse Events Reporting System (VAERS). Further information regarding vaccine adverse event reporting is found at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/VaccineAdverseEvents/default.htm.

The NU IRB requirements for events that may be considered Reportable New Information (RNI) can be found online at https://irb.northwestern.edu/index.html. Those events determined to be Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) be submitted within 5 working days of the event. A UPIRSO is an event that is unexpected, related or possibly related, and suggests greater risk. More information on this policy can be found at https://irb.northwestern.edu/index.html. The Lurie Children's IRB and the Jesse Brown VA Medical center have similar reporting requirements. The Lurie Children's policy is described in the "IRB Policy and Procedures Manual" located online at https://www.luriechildrens.org/en/research/management/research-integrity-compliance/irb/, and the VA Policy is outlined online at http://www.va.gov/ORO/Docs/Guidance/1058_01_Decision_Chart_Rsch_Death_SAE_Problem_09_14_2015.pdf.

If the trial involves behavioral or nutritional interventions that do not use an investigational agent, there are no standard grading scales for adverse events. Therefore, defining suitable grades for adverse events is the responsibility of individual investigators for each protocol. Adverse events of a psychological nature can occur with behavioral trials and should be specified for the particular intervention in question.

MULTI-CENTER TRIAL ADMINISTRATION

The Lurie Cancer Center has established Standard Operating Procedures (SOPs) that are used for the management of multi-center LCC IITs. These procedures include activities related to site qualification, pre-activation, protocol training, trial initiation, and clinical and regulatory communications. Activities related to the Lurie Cancer Center oversight committees are addressed in all these areas and are described below.

6.0 Site Qualification and Trial Initiation

The Lurie Cancer Center has a dedicated Project Manager who provides oversight for our affiliate network and works directly with the network and other sites participating on LCC IITs. Communications related to study start up and ongoing regulatory compliance are directed by this Program Manager.

When the Lurie Cancer Center is informed of a potential new site for an LCC IIT, the multi-site project manager sends the site a packet of information, including the Participating Site Data Compliance Policy. The packet must be completed by each new participating site, and all completed forms are returned to and reviewed by the Multi-Site Compliance Program Manager to determine if a site is a good candidate for the trial. The Project Manager reviews the PI's data delinquency status on other studies, as applicable. If the PI is in good standing and a confidentiality disclosure agreement is in place, the site may be approved and allowed to submit the Lurie Cancer Center IRB approved version of the protocol to their local IRB. Each new site PI must sign and return the Data Compliance Policy before any activity related to a study may begin.

While a participating site is awaiting local IRB approval, other site pre-activation activities may begin. During this time, the multi-site project manager collects required regulatory documents (e.g., signed 1572, financial disclosure forms, medical licenses, contracts, etc.). In addition, a site initiation visit (SIV) is required for all studies (which may be performed by teleconference), and the site will receive training on eCRFs. The site will be activated once all required pre-activation requirements are complete and their documentation of IRB approval has been received.

6.1 Active Trial Communications

Unless an alternate monitoring plan has been approved by the SRC, all sites participating in LCC IITs are expected to comply with this DSMP. As such, all sites will use the Lurie Cancer Center created eCRFs designed for the study. All data are submitted to the assigned QAM, as described in each study. The data is monitored by the QAM and reviewed by DSMC as described in this plan.

Participating site clinical and regulatory data are included in the auditing program. When a participating site case is selected for audit, the site is informed of this and is expected to submit all source documents for inclusion in the audit. In addition, regulatory documents and pharmacy logs must also be submitted for inspection. Sites are expected to comply with all requests of the CTAC.

6.2 Consortium Trials

In the event that in LCC IIT is activated through a consortium, the consortium may elect to use the Lurie Cancer Center's Data and Safety Monitoring Plan as the monitoring plan of record. In such cases, quality assurance activities usually performed by the Lurie Cancer Center Quality Assurance department may be delegated to a Contract Research Organization. Any organization that manages quality assurance activities on such trials must explicitly agree to adhere to the Lurie Cancer Center Data and Safety Monitoring Plan and must report regularly to the Data and Safety Monitoring Committee.

7.0 INVESTIGATOR RESPONSIBILITIES

While the Lurie Cancer Center research oversight committees hold a great deal of responsibility for trial monitoring, the PI of each study is ultimately responsible for every aspect of the design, conduct, and final analysis of the protocol. All PIs are required to complete all institutional training requirements, abide by federal policies and guidelines, and abide by those commitments outlined in FDA Form 1572/Investigator Agreement. In addition, the study PI must ensure that:

- All protocols include a data and safety monitoring plan (either this plan or a plan developed by the PI and approved by the SRC).
- All studies have a structured adverse event determination, monitoring, and reporting system,

including standardized forms and procedures for referring and/or treating participants experiencing adverse events.

- The proposed schedule for reporting adverse events to the QAMs, IRB, and appropriate federal agencies is described in the protocol.

- In specific cases where an outside agency is the sponsor of the test agent, (i.e., holder of the IND), PIs must submit individual adverse event reports to the funding agency/sponsor in accordance with sponsor and FDA regulations.

- With the assistance of CTO staff, participating sites enrolling in multi-center trials are kept informed of unanticipated SAEs and/or any problems identified by the DSMC or IRB.

- Semi-annual reports are reviewed and per DSMC guidelines.

- The appropriate committees of the research oversight system and applicable personnel are informed of actions, if any, taken by the IRB as a result of Continuing Review or any other IRB submission (e.g., Reportable New Information).

- With the assistance of the CTO regulatory staff (or other personnel if not managed by the CTO), DSMC, SRC and CTAC reports are submitted to the IRB of record per their requirements.

- All decisions made by the research oversight committees are adhered to (e.g., protocol suspensions or closures).

- The informed consent document is complete and accurately reflects the risks and other essential information as part of the initial submission to the SRC. In the event that a waiver of consent will be requested, a justification must be submitted to the IRB.

- All blinded studies describe a randomization scheme and specific criteria and procedures for unblinding.

- All data used for abstracts and publications of LCC IITs have been reviewed and approved for release by the DSMC.

- In the case where the Lurie Cancer Center PI is an IND/IDE holder, all FDA reporting requirement to maintain the IND/IDE are followed. This is done with the assistance of the QAMs.
- In accordance with NIH policy released September 22, 2000 entitled “Notice To NIH Grantees/Contractors Regarding Letters Or Notices From The Food And Drug Administration (FDA),” the Lurie Cancer Center requires the PI of any IND or IDE trial receiving federal funds to inform the awarding Institute of significant communications from FDA.
- As per NCI requirements, the NCI Program Director responsible for funding a trial must be informed of any communication affecting the status of NCI-sponsored trials (e.g., trial suspension or closure).

- In accordance with federal policy, the PI is responsible for clinicaltrials.gov trial registration and reporting.

Appendix A: Lurie Cancer Center Research Oversight System

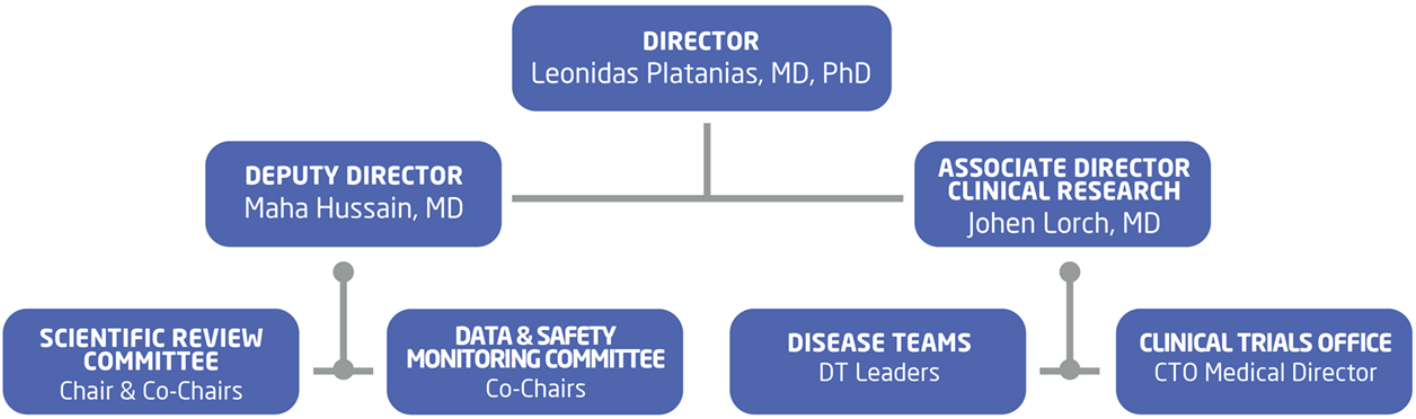

Figure 2: Clinical research oversight structure in the LCC

Appendix B: Lurie Cancer Center Research Oversight System Activity Flow Diagram

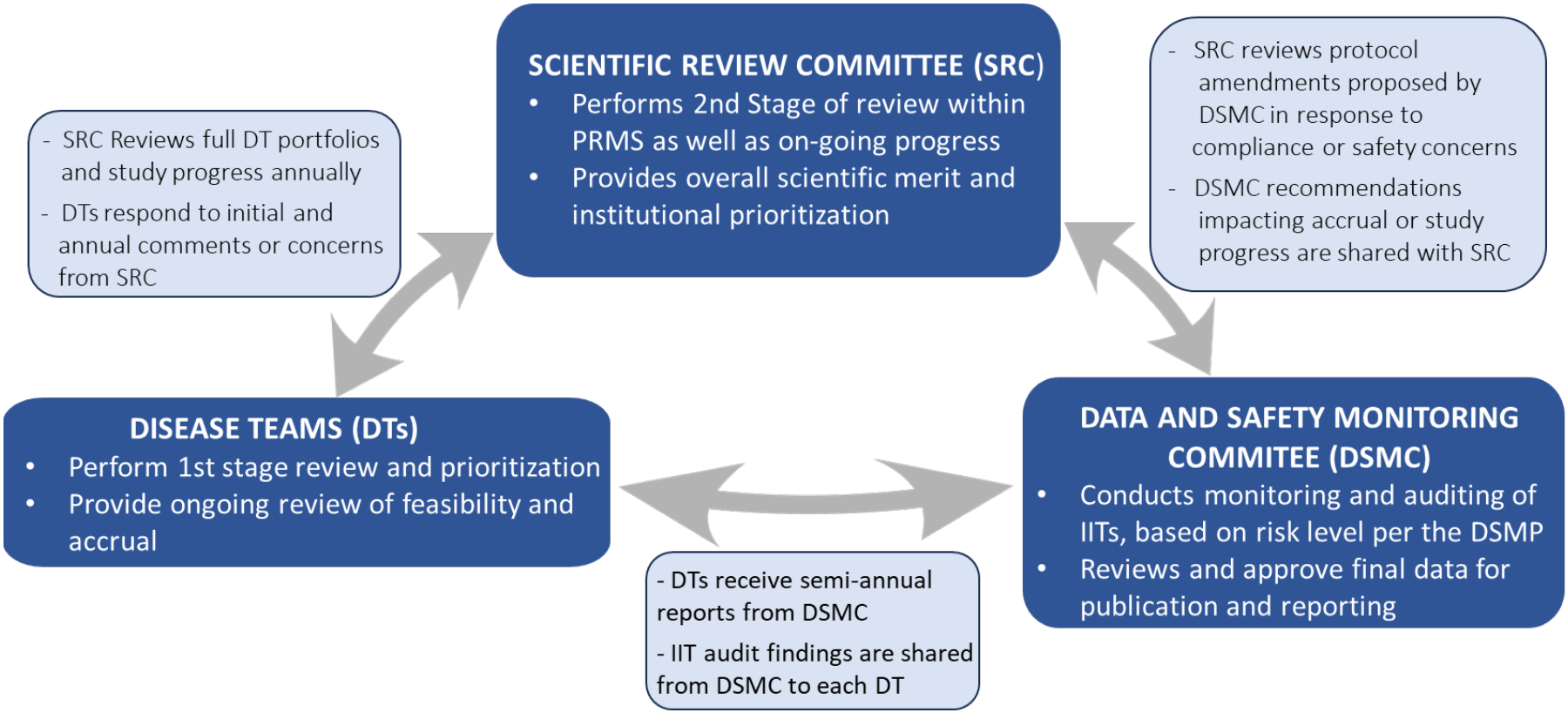

Figure 1: Interactions and communication activities of the LCC research oversight components

Appendix C: Guidelines for the Establishment of Data and Safety Monitoring Boards (DSMBs)

Medical Intervention Clinical Trials

DSMB composition should meet the minimum requirements set forth by the NCI.

https://www.hhs.gov/guidance/document/nci-policy-data-and-safety-monitoring-clinical-trials

https://grants.nih.gov/policy/humansubjects/policies-and-regulations/data-safety.htm

External DSMBs will be reviewed by SRC and final listing of membership and complete DSMB charter should be sent to SRC.CCSG@northwestern.edu

1. The DSMB members, including the chair, must agree to serve on the board. Their approval should be documented and maintained in the trial files.

2. The PI will work to create a DSMB Charter, outlining the requirements and expectations of the DSMB.

    a. The charter should include the name, credentials, and contact information for each member.

    b. It is also recommended that the administrative assistant contact information for each member is provided as well.

    c. The charter should include information on the release of data, confidentiality and conflict of interest

3. Prior to activation, the DSMB should understand their obligations on the board, as defined by the protocol and/or DSMB charter

Non-Medical Intervention Clinical Trials

In instances in which the funding source and/or the NU or LCH COI management plans requires it, a trial may form an independent Data and Safety Monitoring Board (DSMB)..