Data and Safety Monitoring Plan

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**Abbreviations**

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<tr>
<td>AER</td>
<td>Adverse Event Report</td>
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<td>CAPA</td>
<td>Corrective Action and Preventative Action Plan</td>
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<td>CFR</td>
<td>Code of Federal Regulations</td>
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<td>COI</td>
<td>Conflict of Interest</td>
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<td>CRO</td>
<td>Lurie Cancer Center Clinical Research Office</td>
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<td>Clinical Trial Audit Committee</td>
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<td>CTEP</td>
<td>Cancer Therapy Evaluation Program</td>
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<td>CTEP Adverse Event Reporting System</td>
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<td>DCTD</td>
<td>Division of Cancer Treatment and Diagnosis</td>
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<td>DCP</td>
<td>Division of Cancer Prevention</td>
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<tr>
<td>DLT</td>
<td>Dose-limiting Toxicity</td>
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<td>DMC</td>
<td>Data Monitoring Committee</td>
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<td>Data and Safety Monitoring Board</td>
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<td>DSMP</td>
<td>Data and Safety Monitoring Plan</td>
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<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
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<td>FSM</td>
<td>Feinberg School of Medicine</td>
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<td>Health Insurance Portability and Accountability Act</td>
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<td>IDE</td>
<td>Investigational Device Exemption</td>
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<td>IIT</td>
<td>Investigator-Initiated Trial</td>
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<td>IND</td>
<td>Investigational New Drug</td>
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<td>LCC IIT</td>
<td>Lurie Cancer Center investigator-initiated trial</td>
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<td>NOTIS</td>
<td>Northwestern Oncology Trial Information System</td>
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<tr>
<td>NU</td>
<td>Northwestern University</td>
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<tr>
<td>PI</td>
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<td>Quality Assurance Monitor</td>
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<td>Quality Control Manager</td>
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<td>Rehabilitation Institute of Chicago</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SIM</td>
<td>Study Implementation Meeting</td>
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<td>SITC</td>
<td>Site Initiation Telephone Conference</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>Scientific Review Committee</td>
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<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<td>UPIRSO</td>
<td>Unanticipated Problems Involving Risks to Subjects or Others</td>
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<tr>
<td>VAERS</td>
<td>Vaccine Adverse Events Reporting System</td>
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* Please note: through this document, all references to online documents can be found on the Lurie Cancer Center website at [www.cancer.northwestern.edu/ROS](http://www.cancer.northwestern.edu/ROS).
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 First in Human (FIH) and Phase I trials 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.

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 Lurie Cancer Center members, including faculty of the Ann & Robert H. Lurie Children’s Hospital of Chicago (Lurie Children’s), and NU faculty conducting cancer-relevant clinical research within Northwestern University, Northwestern Medicine, the Rehabilitation Institute of Chicago (RIC), the Jesse Brown VA Medical Center (JVBAMC) 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 required to submit a DSMP to the SRC for approval. If the originating site does not have a plan 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 publically 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 must report all conflicts annually. These must be reviewed by the faculty member’s respective school to determine if serious financial COI exists. If it does, the school will work with NU personnel to develop a plan to manage, reduce or eliminate 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’s research oversight committees abide by 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 cancer center Director, Associate Director for Clinical Science Research and/or applicable committee leader). 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.

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 a protocol on which he or she serves as a Principal Investigator (PI) or sub-investigator. When a trial investigator is present at a meeting and his or her protocol is being discussed in consideration for initial approval, he or she is required to leave the meeting during the discussion and the vote on the project. The investigator is allowed to be present during discussion related to protocol revisions or data and safety monitoring issues; however, he or she may not vote on these items. He or she may also not serve as an auditor for his or her own trial.

- 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. This will be determined by the committee chair and/or co-chair. Those individuals found by the chair and/or co-chair to have a significant conflict related to a trial will not be allowed to vote on items related to that trial, as described above.

2.4 Confidentiality

All discussions that occur within any of the Lurie Cancer Center 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 committees, as appropriate, on behalf of the entire committee via a meeting coordinator, but no specifics are given related to the persons involved or details of the discussion that occurred. Any paper materials distributed during committee meetings are collected and destroyed after each meeting.

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 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. This plan applies only to clinical trials, as defined in section 2.2 of this document and include studies supported through various funding mechanisms, including competitive NCI/NIH grants, other agency/sponsor grants or gifts, and grant-in-aid support from industry sponsors.
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. The level of risk is assigned irrespective of the type of intervention under consideration (e.g., therapeutic, prevention, supportive care, etc.), and all clinical trials that fall under the purview of this plan are assigned a level of risk. The level of monitoring required will correspond with the level of risk assigned. A variety of factors are taken into consideration in making this determination, such as the size, expected duration and complexity of a trial, the trial phase, safety measures included in the study design, study population, and the toxicity profile associated with the agent under investigation. In the event that a study may be reasonably assigned to two categories, the highest risk category will be selected. The levels of risk and associated monitoring are:

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<th>Monitoring Level</th>
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<td><strong>Minimal Risk</strong> – 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.</td>
<td><strong>Low Intensity Monitoring</strong> – This level applies to those studies that do not include a physical intervention with a participant. An example of this type of trial is a computer or internet-based strategy aimed at increasing awareness of cancer issues. Monitoring by the Data Monitoring Committee (DMC) is not required for these studies. OR</td>
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<td><strong>Moderate Risk</strong> – 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.</td>
<td><strong>Moderate Intensity Monitoring</strong> – An example of this type of trial is a topical agent used to control a drug rash. For these trials, the PI is required to submit adverse event CRFs/eCRFs to the QAMs in real time. Accrual is reported at each DMC meeting (semi-monthly). DMC monitors these studies semi-annually through review of semi-annual reports.</td>
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<td><strong>High Risk</strong> - 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.</td>
<td><strong>High Intensity Monitoring</strong> – This level of monitoring applies not only to clinical trials categorized as High Risk, but also to any clinical trials for which an NU investigator hold the IND/IDE. An example of this type of trial is a chemotherapy trial aimed at treating cancer. DMC monitoring of these studies is rigorous; reported SAEs are</td>
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reviewed at the next scheduled DMC meeting and safety reviews are done in real time and are ongoing. For phase I studies, safety data are presented in total after each cohort is complete. Outcome data are presented as required by the design of protocol or is request by the PI or DMC. For phase II and III studies, safety and outcome data are reviewed in total at least semi-annually, and may occur more frequently if issues arise. The DMC conducts a comprehensive review of study progress semi-annually through review of semi-annual reports.

3.2 Data and Safety Monitoring Boards

Clinical trials for drugs or devices that were developed from lab work done within the Lurie Cancer Center are subject to more extensive monitoring, to ensure that COI is avoided. All such trials are required to follow the DMC requirements for High Intensity Monitoring. In addition, they have the further requirement of establishing an independent Data and Safety Monitoring Board (DSMB). Composition of this board must be proposed by the study PI and approved by the DMC.

Phase III medical intervention trials are required to follow the DMC requirements for High Intensity Monitoring. In addition, they have the further requirement of establishing an independent Data and Safety Monitoring Board (DSMB). Composition of this board must be proposed by the study PI and approved by the DMC.

Clinical trials that do not involve a drug or device intervention may require the establishment of an independent DSMB if required by the funding sponsor. These studies may present low to moderate risk, but additional safeguards are deemed necessary to ensure the trial is progressing acceptably. For example, the study may be comprised of several phases, each requiring data analysis prior to movement into the next phase. In a case such as this, an independent board is required to ensure an unbiased review of the data.

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 comprise the Center’s Protocol Review and Monitoring System (PRMS). The Data Monitoring Committee (DMC) and the Clinical Trial Audit Committee (CTAC) are responsible for data safety monitoring. The committees are independent and report directly to the Lurie Cancer Center Deputy Director. The Deputy Director, in turn, reports to the Director of the Cancer Center. Each committee or team includes a leader and co-leader. All leaders are appointed for two-year terms renewable for exemplary performance. 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 Disease Team is to provide an integrated, multidisciplinary approach to guide in the selection and prioritization of high quality cancer research studies. Each Disease Team includes a team leader and co-leader, responsible for proper functioning of the team. A listing of Disease Teams and their associated leaders may be found online at Disease Team listing.

The Disease Teams meet at least monthly to review all new studies under the purview of their team. Disease Teams must first endorse each new study before the protocol may be submitted to the SRC. The SRC, DMC and CTAC communicate with the Disease Teams, as needed, and will inform a Disease Team of any issues or concerns raised before those committees that impacts the research portfolio of the Disease Team. DMC will regularly send semi-annual reports for each monitored study and, CTAC will provide copies of all audit reports, to the Disease Team.

4.2 Scientific Review Committee (SRC)

The SRC is charged with the responsibility of evaluating new and ongoing clinical research protocols for scientific merit and institutional priority and for ongoing monitoring of trials, including review of accrual 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 Alfred Rademaker, Ph.D. and Sunandana Chandra, MD. Dr. Chandra has specific responsibility for the SRC expedited review process. A full member listing is included online at SRC membership.

SRC review includes a two-stage design for LCC IITs; first the committee reviews a Letter of Intent (LOI), then the full protocol. The SRC assigns level of risk to LCC IITs during LOI review. Investigators are responsible for ensuring language in the protocol describes appropriate monitoring, based on the level of risk that is assigned. This decision is communicated to the DMC. Upon review of a full protocol, the SRC reviews the adequacy of data and safety monitoring plans in every protocol, and will not approve protocols that do not include an adequate DSMP. During ongoing progress review, SRC will notify the DMC regarding any decisions that impact protocol status (e.g., suspension or closure) for those studies under DMC purview.

The DMC is responsible for informing the SRC of any findings that may impact the scientific integrity of a trial, and SRC reviews any such reports at the next scheduled SRC meeting. In the event that the committee is notified of misconduct or other issues impacting study integrity the SRC will contact all appropriate authorities as needed (e.g., the IRB, FDA, NCI, funding sponsor, etc.). In the event that a suspension or closure occurs on an NCI funded trial, the SRC will ensure the PI reports this the NCI Program Director.

4.3 Data Monitoring Committee (DMC)

The DMC plays an integral role in data and safety monitoring. 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 with additional representation from 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. Olga Frankfurt, M.D. serves as chair of the committee and Sonali Chaudhury, M.D. is the co-chair. A full member listing is found online at DMC membership.

The Assistant Director for Administration of the Lurie Cancer Center provides oversight of the administration of the committee and also acts as a liaison between other clinical research oversight committees, investigators, and the Lurie Cancer Center Clinical Research Office (CRO). The Lurie Cancer Center’s Quality Assurance
team provides administrative support for the committee, and each study monitor is responsible for reporting trials they monitor at semi-monthly DMC meetings. Their review specifically focuses on participant safety and toxicity, outcomes/response, accrual updates, compliance issues, and overall data integrity (see sections 5.0 for more information related to monitoring activities).

The DMC is an independent committee responsible for safety review and study progress monitoring for Lurie Cancer Center investigator-initiated clinical trials. While the DMC is a distinct independent committee, DMC shares its findings with the other committees of the Research Oversight System, as needed. In particular, DMC will notify SRC of any issues they believe to be potentially relevant to the scientific integrity of the trial. The DMC will also communicate with Disease Teams, informing them of any concerns, and regularly sends the team leaders semi-annual reports for relevant LCC IITs.

The DMC meets semi-monthly and provides the following:

- **Safety review**: DMC conducts ongoing safety reviews of all LCC IITs requiring moderate and high intensity monitoring, and semi-annual safety reviews for those studies determined to require minimal, moderate or high intensity monitoring. Safety review includes a listing of all reportable adverse events, as specified in each protocol, that occur on the trial. The DMC has the authority to suspend or close any study if serious safety concerns are identified. If the decision is made to suspend or close a study, this change is made by the study assigned Quality Assurance Monitor (QAM) within the Lurie Cancer Center’s clinical trials management system (NOTIS), and this generates an automatic notice of study status change to the PI and study team. In the event that a suspension or closure occurs on an NCI funded trial, the DMC will ensure the PI reports this to the NCI Program Director.

- **Ongoing study monitoring**: DMC reviews the progress of all LCC IITs through review of semi-annual reports, required for all clinical trials monitored by the committee. The semi-annual reports include such information as accrual, reported adverse events, and compliance issues. Full report templates for the DMC Semi-Annual Report and the DMC Minimal/Moderate Semi-Annual Report may be found online at [DMC Semi-Annual Report Templates](#). If the DMC finds that study progress is not meeting the requirements of the Lurie Cancer Center Low Accrual Policy (see Low Accrual Policy) or in the event there is an issue with regards to the scientific progress of the study, SRC will be notified of the concern.

- **Review of audit findings**: DMC reviews audit reports submitted by CTAC. In particular, CTAC submits audit reports and corrective and preventative action plans (CAPAs) to the DMC for any audit findings that relate to data integrity or patient safety. The DMC has the authority to require further corrective action if the submitted plans are determined to be insufficient to address the findings. The DMC further has the authority to suspend or close the trial in the event that major concerns are found during an audit. If the decision is made to suspend or close a study, this change is made by the study assigned QAM within the Lurie Cancer Center’s clinical trials management system (NOTIS), and this generates an automatic notice of study status change to the PI and study team.

- **Serious adverse event (SAE) review**: DMC reviews all SAEs that occur on trials monitored by the committee. The study assigned QAM reports the individual events at the first DMC meeting after receipt of the event report. These events are also incorporated into each protocol safety review/adverse event summary table, which is regularly reviewed by the DMC (as described in the first bullet point, above).

- **External Suspected Unexpected Serious Adverse Reaction (SUSARs) review**: The DMC reviews SUSARs for all LCC IITs monitored by the DMC and for which a Lurie Cancer Center investigator holds the Investigational New Drug Application (IND) or Investigational Device Exemption (IDE).
These events are compiled for each study and are reviewed at least quarterly. Those events that meet IRB reporting requirements are routed to the IRB. For multi-institutional Lurie Cancer Center trials, reportable events are sent to participating sites as a Safety Reports, and modified consent documents are sent as needed.

- Dose Limiting Toxicity (DLT) review: DMC reviews all potential DLTs for Phase I dose-escalation studies. The study assigned QAM reviews all toxicity during the dose-escalation phase of studies and presents this data to the DMC. Protocol suspensions and re-opening of accrual to the next cohort, based on DLT evaluation, fall under the purview of DMC. If the decision is made to suspend or re-open a study, this change is made by the study assigned QAM within the Lurie Cancer Center’s clinical trials management system (NOTIS), and this generates an automatic notice of study status change to the PI and study team.

- FDA report review: DMC is responsible for the review of all FDA annual reports prior to submission to the FDA for those studies where the Lurie Cancer Center PI holds the IND or IDE. Study assigned QAMs work directly with PIs on preparation of all reports to the FDA.

- Protocol deviation review: QAMs review all protocol deviations, and those determined to potentially be reportable to the IRB are reviewed at a DMC meeting (this form may be found at Protocol Deviation Form). If the DMC determines a deviation is reportable to the IRB, the QAM communicates this information to the study’s assigned regulatory coordinator and study team, and they work together to submit this to the IRB.

- Data set review: QAMs are responsible for reviewing all data for trials that fall under this plan, and for presenting this data to DMC as described in this section. Data to be used for abstract and/or manuscript development must be reviewed and approved by the DMC prior to release to the study PI and/or biostatistician.

- If in the course of its work the DMC finds that the scientific integrity of a trial is in question, this is immediately communicated to the SRC. The DMC will also assist the SRC in reporting this to authorities as needed (e.g., the IRB, FDA, NCI, funding sponsor, etc.).

- In the event that any issues are identified with a trial, the DMC notifies the PI of the issue(s) and may request a response or a more formal Corrective and Preventative Action Plan (CAPA).

4.4 Clinical Trial Audit Committee (CTAC)

The CTAC is responsible for overseeing the conduct of the Lurie Cancer Center’s auditing program. The committee consists of members providing expertise in clinical oncology and research compliance and forms a diversified group of professionals able to provide rigorous oversight of auditing activities. This committee is chaired by Jessica Altmann, M.D. and co-chaired by Cesar Santa-Maria, M.D. A full member listing is provided online at CTAC membership. CTAC responsibilities include:

- Audit scheduling and conduct: CTAC schedules audits, assigns auditors, and ensures audits are conducted as required by the Lurie Cancer Center SOP on auditing of IITs. CTAC leaders are available to advise on audit activities, answer questions as needed, and attend key audits, as needed.

- Review of audit findings: CTAC reviews all audit findings and makes the final determination on the seriousness of issues identified during the audit. Individual findings are categorized as “lesser” or “major”, following NCI CTEP definitions. The committee will determine if the PI must submit a Corrective and Preventative Action Plan (CAPA), assesses the final audit outcome, and recommends
measures for the subsequent audits.

- Cause-specific review of audits with major violations: CTAC pays particular attention to major and recurrent audit findings and has the authority to suspend study accrual for continued non-compliance. If the decision is made to suspend a study, this change is made by the study assigned QAM within the Lurie Cancer Center’s clinical trials management system (NOTIS), and this generates an automatic notice of study status change to the PI and study team. In the event that a suspension occurs on an NCI funded trial, CTAC will ensure the PI reports this to the NCI Program Director. The committee communicates findings to the DMC and may:
  
  o Recommend that the DMC close a study to further accrual;
  
  o Recommend membership termination for a site due to substandard performance; and
  
  o Recommend changes to policy, protocols, or procedures based on cumulative audit findings.

- Administrative activities: CTAC advises leadership on audit-related activities, outcomes, and policy issues. They also assist in the development of quality assurance tools, measures and SOPs. Audits are conducted following the NCI’s Clinical Trials Monitoring Branch Auditing Guidelines. Lurie Cancer Center audit categories include:

  - Comprehensive Audits – These are semi-annual audits of studies that require high intensity monitoring and that accrued at least one participant since the prior audit. At least one case, or 10% of all accrual, whichever is greater, accrued since the previous audit is chosen. Full audit reports are submitted and reviewed by CTAC at the semi-annual CTAC meeting. These are complete study audits that include, as applicable to the trial, a review of:
    
    o Regulatory compliance (consent content and IRB submissions);
    
    o Drug accountability and pharmacy inspection;
    
    o Shared resource documentation (e.g., Pathology Core Facility, Pharmacokinetics Core, etc.);
    
    o Case review, including a review of protocol compliance (participant consent, eligibility, treatment administration, monitoring for adverse events and outcomes). This review includes source document verification;
    
    o Adverse event reporting, focusing on identification of serious adverse events; and
    
    o Data quality review.

  - First Participant Audits – These are done on both the first Lurie Cancer Center participant to enroll on a new trial and also the first participant enrolled on a new trial at each affiliate. Single-Case Audit reports are batched and presented at the next CTAC meeting, unless major violations are found or if the next CTAC meeting is greater than 3 months away. In this case, the audit report is sent to the committee via email. The case audit occurs after the first participant has completed two cycles or two months of therapy, or goes off active treatment, whichever comes first.

  - For Cause Audits – Typically these audits are the result of suspected or reported non-compliance. Requests for this type of audit are reviewed and approved the CTAC or the Director. These audits may occur at any time and advanced notice is not required. For Cause Audit reports are sent to CTAC
and Lurie Cancer Center senior leadership via email upon completion of the audit.

CTAC meets at least semi-annually, following the Comprehensive Audits. Unless the Committee chairs request additional meetings, review following other audits is done via email or audit reports are batched and presented at the next scheduled CTAC meeting. While CTAC oversees the audit process, the committee itself is not primarily responsible for the actual conduct of the audits. Instead, the Lurie Cancer Center’s Quality Control Manager (QCM), who is an administrative/non-voting member of CTAC, assembles an independent audit team for each audit, including faculty members, fellows, nursing staff and CRO. 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.

After each audit is complete, audit worksheets are collected by the QCM who generates an Audit Report (available online at Internal Audit Report Template). CTAC reviews and finalizes the Audit Report and determines if a CAPA is required of any study team. All CAPAs are then reviewed by CTAC. The CTAC approved Audit Report is then sent to the DMC for review, and any questions or concerns related to audit findings are discussed at the next scheduled DMC meeting. The DMC is responsible for reporting any findings that affect the scientific integrity of the trial to the SRC.

4.5 Lurie Cancer Center Research Oversight Committees and the IRB

NU and Lurie Children’s each have independent IRBs but also share one combined Lurie Children’s /NU IRB panel. RIC is contracted to use the NU IRB. The NU IRB Office supports six IRB panels that each meet monthly. The Lurie Children’s IRB Office provides support for one panel that meets monthly. NU faculty may also use a central IRB. 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.

The SRC and the 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 the protection of study participants from research risks. 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).

5.0 Quality Assurance Monitoring

The Lurie Cancer Center has made it a priority to continuously strengthen our internal quality assurance program. Quality assurance and quality control is an independent office within Lurie Cancer Center, reporting administratively to the Assistant Director of Administration of the Cancer Center. To ensure adequate quality controls at all levels of clinical research has required the interaction of a number of Lurie Cancer Center employees, oversight by the DMC and CTAC, and the participation of the Biostatistics Core Facility. Currently there are two procedures in place for quality oversight: quality assurance review and internal audit, which is overseen by CTAC.

5.1 Quality Assurance Review

Quality assurance review is the responsibility of five Quality Assurance Monitors (QAMs) who report directly to the office’s Quality Control Manager (QCM). 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 all data submitted for trials in real time and they interact directly with each study PI as issues arise. They also work directly with treating physicians and study coordinators, both at the Lurie Cancer Center and at participating sites, if there are issues related to study participants and/or data submission. The QAMs regularly report all findings directly to the DMC during semi-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 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 study. To ensure appropriate forms are used for each study, the QCM and QAMs thoroughly review each new project, and revisions to ongoing projects, to determine eCRF needs. This review includes discussion with the study PI, biostatistician, study coordinator, data manager and/or other study team members to review study objectives, eligibility requirements and registration process, trial design, treatment plan, adverse event reporting requirements, measurement of outcomes and study parameters. The developed forms are the only CRFs used to collect data, and are used by the QAMs to monitor the study.

The QAMs work closely with faculty and staff throughout the life cycle of each protocol. For multi-center studies, the QAMs also work directly with participating site investigators and research staff. Monitoring of data is a primary responsibility of the QAMs. The intensity of monitoring activities varies by the study assigned risk and associated intensity monitoring level and, within the high intensity monitoring level, by protocol phase. QAM monitoring intensity is as follows:

- **Low Intensity Monitoring** – These studies are exempt for QAM review.

- **Minimal Intensity Monitoring** – For these trials participant enrollment logs and adverse events are submitted to the QA office semi-annually. PIs are not required to submit eCRFs for review. DMC monitors study progress through review of DMC Minimal/Moderate Semi-Annual Reports, which are completed collaboratively by the PI and the assigned QAM (this form may be found online at DMC semi-annual report).

- **Moderate Intensity Monitoring** – This monitoring level is for studies that involve a moderate risk, and more intensive monitoring for adverse events is required. PIs are required to prospectively register participants and submit adverse event eCRFs to the QAMs in real time; other types eCRFs (e.g., response data) are not required. DMC monitors study progress through review of DMC Minimal/Moderate Semi-Annual Reports, which are completed collaboratively by the PI and the assigned QAM (this form may be found online at DMC semi-annual report).

- **High Intensity Monitoring** – These are high-risk trials that require extensive monitoring by QAMS. For these trials, the PI is required to prospectively register all study participants through the QAMs and all eCRFs are submitted to and monitored by the QAMs, per the data submission schedule outlined in the protocol. In addition, the PI must submit all SAEs to the QAMs in real time, as defined by each protocol. These events are reviewed at the next scheduled DMC meeting. Safety reviews for these studies are done in real time and are ongoing. For phase I studies, safety data are presented in total after each cohort is complete. Outcome data are presented as dictated by the design of the trial or if requested by the PI or DMC. For phase II and III studies, safety and outcome data are reviewed in total at least quarterly, and may occur more frequently if issues arise. The DMC conducts a comprehensive review of study progress semi-annually through review of the DMC Semi-Annual
DATA AND SAFETY MONITORING PLAN

5.2 Quality Assurance Activities for High Intensity Studies

The QAMs work closely with faculty and staff throughout the life cycle of each protocol, from initial protocol development through final data analysis and study termination. New LCC IITs requires a Study Implementation Meeting (SIM), which is a meeting that brings together members of the study and extended care teams, to ensure the study is feasible and that the protocol document is clear and easy to follow. The QAMs are important participants in the SIM, providing valuable input on the protocol document, including such things as ensuring registration procedures and other QA activities are adequately described. It is during this early stage that the QAMs also work with the PI and study team to develop eCRFs for the study.

QAM data monitoring activities are most extensive for studies determined to be high intensity. These studies require real-time data capture by the study team. QAMs review eCRFs for all high intensity studies in real time, but the level of QA monitoring of source documents varies by study phase. Monitoring activities are described below.

- Patient Registration – All study participants must be registered prior to beginning study treatment. Study coordinators must complete and submit an eligibility checklist that has been approved and signed by the treating physician, and provide the signed informed consent document and pathology report to the QAM for confirmation of eligibility. Further, all phase I and high-risk pilot protocols also require 100% source document verification of eligibility prior to registration. This is done via access to the electronic medical record, or in the case of participating sites, review of paper source documents. Phase II and III studies do not require source document verification, but this is reviewed when the case is selected for audit.

- Data Submission and Protocol Compliance – eCRFs are designed to capture all endpoint and safety data as defined by the protocol and PI. The eCRFs are submitted and the study-assigned QAM reviews them in real time for completeness and compliance to the protocol. In addition to eCRF review, all phase I and high-risk pilot protocols require 100% source document verification. This is done via access to the electronic medical record, or in the case of participating sites, review of paper source documents. Phase II and III studies are not monitored in real time, but are subject to interim monitoring visits, conducted every 6-8 weeks. These visits include review of all new case report forms completed since the prior monitoring visit. These studies do not require 100% source document verification, but all source documents are reviewed when the case is selected for audit. Data completion timeline requirements vary by protocol, and to ensure proper monitoring of toxicity, particularly for higher risk studies, the DMC has established a Data Compliance Policy that outlines submission requirements (see Internal Data Compliance Policy).

- Toxicity Review – Toxicity data are submitted to the QAMs on the appropriate eCRFs. The QAMs thoroughly review reported toxicity for participant safety and outcomes and report all SAEs, DLTs and unusual or frequent toxicities at the DMC meetings as part of their ongoing safety reviews. All phase I and high-risk pilot protocols require 100% source document verification. This is done via access to the electronic medical record, or in the case of participating sites, review of paper source documents. Phase II and III studies do not require source document verification, but this is reviewed when the case is selected for audit. In either case, the QAMs provide complete lists of adverse events, including the grade and attribution of each event, that have occurred on a trial, allowing DMC to provide a comprehensive review of toxicity with the goal of identifying unexpected trends in toxicity. If, in the course of this review, any unexpected patterns in events are seen, the DMC may take action, such as requiring trial suspension, closure or modification. If the decision is made

Report, which is completed collaboratively by the PI and the assigned QAM (this form may be found online at DMC semi-annual report).
to suspend or close a study, this change is made by the study assigned QAM within the Lurie Cancer Center’s clinical trials management system (NOTIS), and this generates an automatic notice of study status change to the PI and study team. If the QAMs see any unexpected patterns of events during the course of their ongoing safety monitoring, this is presented to the DMC immediately. In addition, all SAEs that occur on these trials, including the PI assessment of the event, are reviewed by the DMC at the next meeting. SAEs are followed until resolution.

- Expedited Adverse Event Reports (AER) – The QAMs review submitted data to determine if an expedited AER is required, and if so, if the report was submitted in a timely fashion and in the correct format. AER review includes a comprehensive review of the SAE form and supporting source documentation. These events are presented at the next scheduled DMC meeting and are followed through resolution.

- Response Review – The QAMs review all response data to ensure that response is evaluated and reported correctly. All phase I and high-risk pilot protocols require 100% source document verification. This is done via access to the electronic medical record, or in the case of participating sites, review of paper source documents. Phase II and III studies do not require source document verification, but this is reviewed when the case is selected for audit. Response data are reported to the DMC at intervals specified by the protocol (e.g., interim analysis) or when data are required by the PI for abstract or publication.

- FDA reporting – For those studies for which the Lurie Cancer Center PI holds the IND/IDE, the QAM assists the PI in creation of the annual FDA report. This report is reviewed and approved by the DMC prior to FDA submission.

- Abstracts and publications – The QAMs present all data used in the study analysis to the DMC for review and approval prior to release of the data to the PI and biostatistician. The QAMs continue to work closely with the study PI and biostatistician during the development of all published materials.

- Clinicaltrials.gov – The QAMs provide all required data to the PI for results reporting in clinicaltrials.gov.

5.3 Adverse Event Reporting Requirements

Adverse event reporting requirements and timing of reporting are dependent on the phase of the trial, 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. In the event that a participant experiences an unexpected event or SAE, the SAE report must be submitted to the CRO, QA office, IRB, and federal agency, as applicable, 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.

All Serious Adverse Events 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.

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://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1397583886412.

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/medwatch/index.html).

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 requires events to be submitted as described in the “Human Subject Protection Program Policy Manual, found at http://irb.northwestern.edu/policies. Those events determined to be Unanticipated Problems Involving Risks to Subjects or Others (UIPRSOs) 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 http://irb.northwestern.edu/process/reportable-new-information. 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-us/research/management/toolkit/irb/Pages/policies-procedures.aspx, 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.

### 6.0 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.

#### 6.1 Site Qualification and Trial Initiation

The Lurie Cancer Center has a dedicated Program 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 managed by this Program Manager.

When the Lurie Cancer Center is informed of a potential new site for an LCC IIT, the Program Manager sends the site a packet of information, including the Participating Site Questionnaire and the Participating Site Data Compliance Policy (found online at Participating Site Data Compliance Policy). The Participating Site Questionnaire must be completed by each new participating site, and all completed forms are routed to and reviewed by the study assigned QAM to determine if a site is a good candidate for the trial. The QAM 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 Program Manager collects required regulatory documents (e.g., signed 1572, financial disclosure forms, medical licenses, contracts, etc.). Site training also begins at this time. The site is provided with all relevant SOPs related to multi-center trials. In addition, a site initiation telephone conference (SITC) is required for all studies, 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.

#### 6.2 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. This data are monitored by the QAM and reviewed by DMC 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.
6.3 Serious Adverse Events

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 DMC. The DMC will review the event and the PI’s Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO) determination form (see section 5.3 and Appendix C for further information). If an event is determined to require expedited reporting to the IRB, it will also be sent to participating sites as a 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 CRO 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 these SUSARs the DMC. Any event determined by the DMC to be a UPIRSO is routed to participating sites for IRB submission and consent and/or protocol modification will be sent to the sites as appropriate.

6.4 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 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. 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 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 the QAMs and Affiliate Program Manager, participating sites enrolling in multi-center trials are kept informed of unanticipated SAEs and/or any problems identified by the DMC or IRB.
- Semi-annual reports are reviewed and submitted per DMC guidelines.

- The appropriate committees of the research oversight system and appropriate staff of the CRO 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 CRO regulatory staff, DMC, SRC and CTAC reports are submitted to the IRB, per IRB requirements.

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

- Protocols include the proposed consent document 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 by the DMC prior to use.

- 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

Lurie Cancer Center Research Oversight System

Faculty Leadership

- Director
- Deputy Director
- PRMS
- DSM
- SRC
- DMC
- Disease Teams
- CTAC

Administrative Support

- Assistant Director, Cancer Center
- PRMS Coordinator
- QA Office
- SRC
- DMC
- Disease Teams
- CTAC

Committee Leadership and Responsibility

Responsibility:

- Initial independent scientific review, interventional trials
- Approval of prioritization, interventional trials
- Ongoing monitoring, interventional trials
  - Scientific changes
  - Accrual
- Administrative review, non-interventional research

Responsibility:

- Administer DSMP
- Release of approved data to PI for abstracts, publication

Responsibility:

- Initial scientific review/interventional trials
- Prioritization, interventional trials
- Dynamic/ongoing accrual review, interventional trials

Responsibility:

- Oversight of audit process
- Review of audit reports
- Review and approve of CAPAs
Appendix B: Lurie Cancer Center Research Oversight System Activity Flow Diagram
Appendix C: Adverse Event Management

Internal Adverse Events

Internal Adverse Event: any adverse event that occurs to any subject at Northwestern University (NU) or any subject at an affiliate on a LCC IIT.

LCC IITs only – Participating Sites

1. SAE occurs at participating site
2. SC completes appropriate AE form: Quality Assurance Monitor (QAM) enters into NOTIS and forwards to LCC PI for UPIRSO consideration.
3. If the event qualifies as a UPIRSO, QAM presents report to DMC. If DMC concurs it is a UPIRSO, QAM distributes report to participating sites.
4. SC files all AE paperwork in the research file(s).

For LCC – All Study Types

1. AE occurs at LCC
2. PI and Study Coordinator (SC) determine event status (UPIRSO, SAE, neither)
3. SC completes appropriate AE form, enters SAE info into NOTIS and forwards to PI for UPIRSO consideration.
4. If the event qualifies as a UPIRSO, SC forwards to Regulatory Coordinator (RC). For NU IITs SC forwards UPIRSOs and SAEs to QAM.
5. RC submits UPIRSOs to IRB and submits revised consents and amendments as necessary within required timeframes. RC updates IRB dates in NOTIS.
6. RC will file all UPIRSOs appropriately.
External Adverse Event Management

SAFETY REPORT FLOW SHEET

Industry Trials and Other External IITs
PI responsible for reviewing all safety reports and forwards those that meet UPIRSO criteria, providing explanation for the impact to the study.

Any report identified by the PI or otherwise received by the Study Coordinator (SC) that meets policy criteria will be forwarded to general SAE mailbox.

NCTN Trials
Admin Assistant monitors NCTN broadcasts, and forwards all events that meet policy guidelines to the SAE mailbox.

Data Assistant Manager enters UPIRSO into NOTIS safety report page and alerts Regulatory Coordinator (RC) of UPIRSO/safety alert.

LCC IITs
QA team is added to safety report mailing lists for LCC IND/IDE studies. Regulatory Coordinators (RC) enter safety reports into NOTIS for these studies. For studies where no IND/IDE is involved, the RC will only enter reports into NOTIS that qualify under AE policy.

RC enters event in eIRB. PI reviews event and submits in eIRB. RC completes UPIRSO tool in NOTIS and saves all files appropriately.

All e-mail is filed according to drug name and the QA dept monitors sub-folders and will report all required events involving NU INDs to DMC, affiliates, and FDA, as required.
Appendix D: Guidelines for the Establishment of Data and Safety Monitoring Boards (DSMBs)

Medical Intervention Clinical Trials

Membership
Phase III trials and trials of drugs or devices developed within a Lurie Cancer Center lab require the establishment of an independent DSMB. The PI of each Phase III study is required to recommend board members to the SRC, who will approve the final board composition. A DSMB is required to consist of six voting members, four of whom are not affiliated with the Lurie Cancer Center. Members should have expertise relevant to the trial and must include:

- Two external physicians.
- One external biostatistician.
- One external behavioral scientist.
- One internal physician.
- One internal biostatistician.

Meetings
DSMB meetings will be held annually, but may be held more frequently depending on the nature and progress of the trial. Each meeting will begin with an open session, where the study PI presents a summary of the trial including current status, toxicity and response. The study biostatistician will present statistical analysis when appropriate. After these presentations and discussions have concluded, the board will meet in closed session to discuss the trial, including blinded results, and make recommendations. All recommendations are provided to the PI and are also submitted to the IRB.

Release of Data
The DSMB may not release outcome data until accrual for the trial has been completed. In the event that data are needed for manuscript preparation or future trial planning, data may be released on a confidential basis.

Confidentiality
All communication of board deliberations are confidential and may not be made available to anyone outside of the board membership, except those public recommendations made by the board.
Non-Medical Intervention Clinical Trials

Membership

Outcomes studies that involve a patient intervention may require the establishment of an independent DSMB. The PI of each study is required to recommend board members to the appropriate disease section leader, who will approve the final board composition. A DSMB is required to consist of a minimum of 4 voting members, all of who are not involved with the study. Members should have expertise relevant to the trial and must include:

- One researcher.
- One biostatistician.
- One clinician.
- A minimum of one additional investigator.

Meetings

DSMB meetings will be held annually, but may be held more frequently depending on the nature and progress of the trial. Each meeting will begin with an open session, where the study PI presents a summary of the trial including current status, toxicity and response. The study biostatistician will present statistical analysis when appropriate. After these presentations and discussions have concluded, the board will meet in closed session to discuss the trial, including blinded results, and make recommendations. All recommendations are provided to the PI and are also submitted to the IRB.

Release of Data

The DSMB may not release outcome data until accrual for the trial has been completed. In the event that data are needed for manuscript preparation or future trial planning, data may be released on a confidential basis.

Confidentiality

All communication of board deliberations are confidential and may not be made available to anyone outside of the board membership, except those public recommendations made by the board.