WINSHIP CANCER INSTITUTE

DATA AND SAFETY MONITORING PLAN

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WINSHIP CANCER INSTITUTE OF EMORY UNIVERSITY
DATA AND SAFETY MONITORING PLAN

VERSION HISTORY

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INTRODUCTION

The Winship Cancer Institute has designed the following Data and Safety Monitoring Plan (DSMP) in order to help ensure the safety of all research participants, the ethical conduct of studies, and the achievement of scientific goals by ensuring high quality data. The DSMP was developed with reference to the FDA Guidance for Clinical Study Sponsors on the Establishment and Operation of Clinical Study Data/Safety Review Committees (http://www.fda.gov/cber/gdlns/clindatmon.htm), the National Institutes of Health Policy for Data and Safety Monitoring dated June 10, 1998 (http://grants.nih.gov/grants/guide/notice-files/not98-084.html) with further guidance issued on June 5, 2000 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). The National Cancer Institute (NCI) issued a policy on June 22, 1999 for data and safety auditing of all studies, with additional requirement that randomized Phase III studies be audited by Data and Safety Monitoring Boards (DSMBs) (http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm). The National Cancer Institute published the essential elements of a Data Safety and Monitoring plan on April 1, 2001: (http://cancerstudies.nci.nih.gov/researchers/dsm/html/essential.html) and provided further guidance for Cancer Centers in September, 2004 (http://www3.cancer.gov/cancercenters/CCSG_Guide12_04.pdf). The Winship Cancer Institute also would also like to acknowledge and thank the many other cancer centers who provided their DSMPs as models. We have freely used their language where appropriate. This specific DSMP, however, reflects the practice at the Winship Cancer Institute.

SCOPE

The Data and Safety Monitoring Committee (DSMC) is responsible for providing oversight to therapeutic/interventional clinical trials conducted by a Winship investigator. Every interventional clinical study conducted through Emory University’s Winship Cancer Institute will have a plan delineated for safety, adverse event reporting, and monitoring. Industry sponsored trials are not under the direct purview of the DSMC. The frequency of monitoring by the DSMC will be dependent upon degree of risk, expected accrual rate, type of study (whether IND/IDE is held by a Winship Investigator), and anticipated safety profile of the investigational interventions. The monitoring frequency will be determined at the outset of the study initiation during the scientific review process, and included in the study protocol, although the committee may monitor more frequently based on ongoing activity and study conduct. For Winship interventional investigator-initiated studies, the protocol-specific monitoring plan will be reviewed and approved by the DSMC. The Principal Investigator is responsible for notifying the DSMC should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval.
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<td>COI</td>
<td>Conflict of Interest</td>
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<td>CAPA</td>
<td>Corrective and Preventive Action</td>
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<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
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<tr>
<td>CRA</td>
<td>Clinical Research Administrator</td>
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<tr>
<td>CRC</td>
<td>Clinical Research Coordinator</td>
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<tr>
<td>CRF/eCRF</td>
<td>Case Report Form/electronic Case Report Form</td>
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<tr>
<td>CRN</td>
<td>Clinical Research Nurse</td>
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<tr>
<td>CTO</td>
<td>Clinical Trials Office</td>
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<tr>
<td>CTRC</td>
<td>Clinical and Translational Research Committee</td>
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<tr>
<td>DLT</td>
<td>Dose Limiting Toxicity</td>
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<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<tr>
<td>DSMC</td>
<td>Data Safety Monitoring Committee</td>
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<td>DSMP</td>
<td>Data and Safety Monitoring Plan</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>ICH-GCP</td>
<td>International Conference on Harmonization-Good Clinical Practice</td>
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<tr>
<td>IDE</td>
<td>Investigational Device Exemption</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>MSC</td>
<td>Multi-Site Coordinator</td>
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<td>NCI</td>
<td>National Cancer Institute</td>
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<td>NCTN</td>
<td>National Clinical Trials Network</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<td>ORC</td>
<td>Office of Research Compliance</td>
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<td>OHRP</td>
<td>Office for Human Research Protections</td>
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<tr>
<td>PI</td>
<td>Principal Investigator</td>
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<td>PRMS</td>
<td>Protocol Review and Monitoring System</td>
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<td>QA/QC</td>
<td>Quality Assurance/Quality Control</td>
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<tr>
<td>QM</td>
<td>Quality Management</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>UP</td>
<td>Unanticipated Problem</td>
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DEFINITIONS

Clinical Studies: Studies involving human participants designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these studies may be patients with cancer or people without a diagnosis of cancer, but at risk for developing cancer. Categories of clinical studies include, but are not limited to, pharmaceutical, medical device, cancer prevention and control, applied, behavioral, epidemiological, genetic, surveillance, survivorship, prevention, detection, human tissue, medical information, supportive care and symptom management. Studies are classified to the following categories based on the National Cancer Institute’s Guidance for Cancer Centers 2004.

Interventional Studies: There are two kinds of interventional studies, therapeutic and prevention.

Therapeutic interventional: Clinical studies with therapeutic intent using drugs, radiation, surgery, and/or biological agents.

Prevention interventional: Clinical studies for the modulation of cancer risk and inhibition of cancer progression using nutrition, dietary or chemoprevention interventions.¹

Non-interventional Studies: Studies in which there are no interventions with the intent to treat or prevent cancer.

Diagnostic Research Studies: Diagnostic studies (such as molecular or imaging diagnostics) are considered to be clinical studies if they use the information from the diagnostic test in a manner that in some way affects medical decision-making for the study participant. In this way, the information from the diagnostic test may have an impact on some aspect of outcome, and the assessment of this impact may be a key goal of the study. By contrast, studies that do not use information from the diagnostic test in any manner that can affect the outcome of study participants, but whose objective is only the gathering of data on the characteristics of a new diagnostic approach are not clinical studies and are not covered by this plan, unless performing the diagnostic test itself imposes some risk on study participants.

Institutional Studies: Institutional studies include both Winship Cancer Institute investigator-initiated studies and multi-site studies that include Winship Cancer Institute investigators that are initiated by an institutional investigator at another academic center.

Investigator-Initiated Studies: Investigator-initiated studies are those authored by a member of the Winship Cancer Institute faculty or staff. Investigator-initiated trials are internally monitored according to this plan.

1.0 ORGANIZATIONAL OVERVIEW

The organizational structure and reporting scheme for the DSMC within Winship Cancer Institute and Emory are outlined below. In summary, the DSMC functions independently within the Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. The DSMC consists of physician investigators, nursing staff, pharmacists and a statistician who review the results of internal monitoring, and full-time staff that monitor individual charts on the studies the DSMC has identified as needing to be monitored. In addition, dedicated administrative staff prepares reports and correspondence in support of the DSMC. The DSMC is distinct in its leadership and organization from the Clinical Trials Office (which consists of staff involved in the conduct of research and associated supervisory personnel), and the Clinical and Translational Research Committee (CTRC).

The DSMC and CTRC have distinct and non-overlapping roles in reviewing clinic research conducted by Winship investigators and separate staff and membership. DSMC and CTRC communicate with each other in matters that are relevant to their respective missions. CTRC’s purpose is to provide scientific oversight for the conduct of clinical research involving cancer patients at Emory University as part of the Protocol Review and Monitoring System (PRMS) for the Winship Cancer Institute. The CTRC is responsible for reviewing all new clinical trials involving cancer patients and subjects at risk for cancer. The level of risk associated with each clinical trial is determined during the CTRC review based on set parameters as outlined in this DSMP. An evaluation of the adequacy of the trial-specific data and safety monitoring plan is done by the DSMC. The DSMC will review and approve the protocol specific monitoring plan for all investigator-initiated interventional studies by a Winship investigator, during the CTRC scientific review process. CTRC approval will not occur prior to the protocol-specific monitoring plan being approved by the DSMC. The Principal Investigator is responsible for notifying the DSMC should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval.

The DSMC review for studies is independent of the internal Quality Management (QM) [Quality Assurance (QA)/Quality Control (QC)] process in effect within the Clinical Trials Office and other processes within Emory University. The DSMC, which has the authority to recommend suspension of accrual to studies with problems in data quality, unfavorable risk-benefit ratio, compliance with Emory policy, or compliance with GCP, communicates these administrative recommendations to the CTRC as suspension to accrual on a specific study will affect the ability of that study to meet its scientific objectives and may affect prioritization of accrual onto competing studies. The CTRC, which has the authority to recommend suspension of accrual of studies that have limited accrual or address scientific questions that have been superseded by new data, communicates these administrative recommendations to the DSMC as suspension to accrual on a specific study will affect the schedule for monitoring. When necessary, communication of monitoring reports from the DSMC to the IRB occurs following review of internal monitoring reports by the DSMC. In situations in which immediate reporting to the IRB is indicated, such as unanticipated problems (UPs), serious adverse events (SAEs) which are life-threatening or fatal, and regulatory non-compliance, the DSMC Chair or designee will assist in expedited reporting to the IRB.

For pediatric studies, the role of Aflac Cancer and Blood Disorders Center’s Data and Safety Monitoring Board (DSMB) is to protect the interests of subjects and the scientific integrity for all therapeutic investigator-initiated clinical trials unless it is provided by another external entity. The DSMB membership consists of five voting members and four ad hoc members, if special expertise is needed. Voting members include physicians, statisticians, other scientists based on their experience and expertise in the design and conduct of pediatric oncology clinical trials. To objectively review trial data and avoid financial influence, DSMB members must be free of conflicts of interest. On a quarterly basis, the DSMB reviews trial safety data for stopping rules, deviations, study amendments, accrual rates and monitoring reports for therapeutic investigator-initiated clinical trials and any other trial as deemed necessary. Ad hoc meetings may be necessary as new safety information becomes available. The Clinical Trials
Coordinator (CTC) will record meeting minutes for all scheduled and ad hoc DSMB meetings. The CTC will distribute meeting minutes to the appropriate parties. For each study reviewed, the DSMB will provide a recommendation for study continuation as planned or suspension. The study’s PI will be notified in writing of recommendations generated during the committee meetings. The Compliance Monitor (CM) will carry out the internal monitoring functions for studies under the DSMB’s purview. The independent review by the CM ensures subject safety and that the trial is conducted in accordance with protocol parameters, GCP, applicable regulatory requirements as well as accurate and complete reporting of data. Components of the monitoring review include informed consent, eligibility, response, toxicity, source documentation compared to case report forms, data entry timeliness, drug accountability, and essential documents. The frequency of internal monitoring is determined by the rate of accrual for the therapeutic investigator-initiated trials. Additional monitoring may be performed if deemed necessary.
2.0 DATA AND SAFETY MONITORING COMMITTEE

2.1 Membership

The DSMC consists of a Chair, Vice-Chair, faculty investigators and support staff. The DSMC is comprised of voting and non-voting members. Voting members consist of medical oncologists, radiation oncologists, at least one non-Winship Cancer Institute Emory faculty member, a research nurse, and a statistician. The Chair and members of the DSMC are appointed by the Director of the Winship Cancer Institute following recommendations from the Associate Director of Clinical Research. The DSMC will request the presence of non-members on an ad hoc basis if additional expertise is necessary for the full review of trial conduct.

Suresh S. Ramalingam, MD is the Chair of the DSMC. He is a Professor of Hematology and Medical Oncology. Dr. Ramalingam serves as the Chief of Medical Oncology at Emory University and the Director of the Thoracic Malignancies Program. He has served as the principal investigator on a variety of clinical trials including Cancer Therapy Evaluation Program (CTEP)-sponsored and cooperative group studies. He is also the Chair of the Thoracic Malignancies Committee at the Eastern Cooperative Oncology Group (ECOG)-American College of Radiology Imaging Network (ACRIN) Cancer Research Group.

R. Donald Harvey, PharmD serves as the Vice-Chair of the DSMC. He is an Associate Professor in the Department of Hematology and Medical Oncology. He has extensive experience in the conduct of Phase I clinical trials. He serves as the Director of the Phase I Clinical Trials Program at the Winship Cancer Institute.

Martha Arellano, MD is an Associate Professor of Hematology and Medical Oncology. She specializes in the treatment of hematological malignancies. She is an active participant in the clinical trials activities for patients with hematological malignancies at the Winship Cancer Institute.

Carlton Dampier, MD, CPI is a Professor of Pediatrics and the Assistant Dean for Clinical Research at Emory University School of Medicine. He also serves as the Medical Director in the Office of Clinical Research. Dr. Dampier is a pediatric hematologist and has been extensively involved in the conduct of clinical trials. He also serves as a representative of the Atlanta Clinical and Translational Science Institute for the Winship DSMC.

Arif Ali, MD is an Assistant Professor of Radiation Oncology. He specializes in the treatment of malignancies of the thoracic and other solid organ malignancies. He is an active participant in NRG Oncology Group studies.

Ms. Stephanie McMillan, RN, BSN, OCN is a Clinical Research Nurse at the Winship Cancer Institute at the Emory Midtown Hospital. She has extensive experience in the regulatory aspects and the conduct of studies.

Michael Kutner, PhD is a biostatistician and former Chair of Biostatistics at Emory University Rollins School of Public Health. He is a highly respected scholar with many years of experience with clinical trials at Winship Cancer Institute.

Thomas Cash, MD, MSC is an Assistant Professor in pediatric hematology and medical oncology. He is actively engaged in the conduct of early phase clinical trials at Children’s Healthcare of Atlanta.

Katherine Shah, PharmD, BCOP is a clinical specialist in hematology and medical oncology with a focus on quality and safety at Winship Cancer Institute. She is the Chair of the Oncology Pharmacy and Therapeutics Subcommittee and Chemotherapy Quality and Safety Council.

Vamsi Kota, MD is an Assistant Professor of Hematology and Medical Oncology. He is an active participant in the clinical trials activities for patients with hematological malignancies at the Winship Cancer Institute.
Stephanie deRijke, RN, MSN, FNP, CIP is the Director for Emory University’s Clinical Trials Audit and Compliance Department. She has extensive clinical research experience which includes serving as an investigator of gastroenterology trials at the NIH Clinical Center. In addition, she previously worked to develop the Emory Institutional Review Board Education and Quality Assurance program.

2.2 Conflict of Interest

DSMC members are subject to Emory’s Conflict of Interest Policy. Members of the DSMC may not have any other professional or personal involvement with the study that they are overseeing, such as serving as a principal investigator, co-investigator, research coordinator, or as a study subject. Individuals invited to serve on the DSMC as either voting or non-voting members will disclose any potential personal, professional or financial conflicts of interest, whether real or perceived, and will abide by the Emory University’s Conflict of Interest policy found at http://www.coi.emory.edu/policies/index.html. In addition, financial conflicts of interest must be disclosed to the Conflict of Interest Review Office as indicated by Emory’s policy. DSMC members with a conflict of interest will recuse themselves from any deliberations or administrative review responsibilities for the study with which they are conflicted. This recusal will be documented in the meeting minutes. In the cases in which the Chair is conflicted, a non-conflicted DSMC member will assume responsibility for administrative review of the study in question.

2.3 Meetings

The DSMC convenes on a monthly basis and voting member quorum is required for all monthly meetings. Quorum consists of at least four voting members. During the meetings, the DSMC reviews available aggregate safety data, monitoring report findings with investigator responses in addition to any other supplemental material provided by the investigator that may assist with ensuring an accurate review of the data and safety of the trial. If non-member expertise is warranted for a particular trial during a monthly meeting, the individual will not be present during any DSMC discussions or deliberations in order to maintain confidentiality. Meeting minutes will be prepared by the designated administrative support staff or a member of the monitor team. The designated administrative support staff or a member of the monitor team is responsible for maintaining and archiving meeting minutes. Minutes are reviewed and approved by voting members at each monthly meeting. Ad hoc meetings are held to address specific issues that require immediate attention for assurance of subject safety. For decisions regarding dose escalation in Phase I trials, the committee reviews requests and votes electronically on an ad hoc basis.

2.4 Responsibilities

In addition to a comprehensive review of available toxicity data, the DSMC reviews all internal monitoring reports of trials under its purview and requests a corrective and preventive action plan (CAPA) from the PI for identified significant trial conduct deficiencies when necessary. The frequency of monitoring studies by the DSMC is determined through risk assessment. Monitoring frequency will be determined at the outset of the CTRC review and included in the study protocol, although the DSMC may determine to monitor a study more frequently based on ongoing activity and study conduct. The Principal Investigator is responsible for notifying the DSMC should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval. For studies under the DSMC’s purview, the protocol-specific monitoring plan must be commensurate with guidance outlined in this DSMP; the responsibility for approval of these monitoring plans resides with the DSMC. Any major irregularities in the conduct of a clinical trial or compliance with study protocol will be reported by the monitors to the DSMC for review. The DSMC Chair will notify, in writing, the PI and the Winship Associate Director for Clinical Research of any findings that could be considered an unanticipated problem (UP) involving risk to subjects or others, or serious or continuing non-compliance that affects the rights, welfare, or safety of current or future subjects.
Examples of such problems include data insufficiency or data inaccuracy that compromises the scientific validity of the study; serious non-compliance in the conduct of the study or regulatory requirements; or significant deviations in Good Clinical Practice (GCP). Deficiencies in data quality or data completion that could affect the scientific validity of the study will be communicated to the Chair of the CTRC for review by the PRMS.

In the event of major protocol violations, significant or ongoing non-compliance, unfavorable risk-benefit ratio to study participants, or potential unanticipated problems involving risk to subjects or others the DSMC may recommend trial suspension or termination. The DSMC Chair is responsible for notifying, in writing, the recommendation of suspension or termination to the PI and the Winship Associate Director for Clinical Research. The PI is responsible for providing the written DSMC recommendation to the IRB in a timely manner. A decision to halt accrual or all research activities will be made by the Winship Associate Director for Clinical Research and will be reported, in writing, to the PI, IRB, the Winship Cancer Institute Director, the NCI and the relevant cooperative group (when applicable), and other regulatory agencies as needed. The Winship Associate Director for Clinical Research has the authority to terminate trials for cause. If the Winship Associate Director for Clinical Research decides to accept the DSMC recommendation for trial termination, the Winship Associate Director for Clinical Research will communicate the decision in writing to the PI, IRB, the Winship Cancer Institute Director, the NCI and the relevant cooperative group (when applicable), and other regulatory agencies, as needed.

Serious findings related to deficiencies with protocol compliance, regulatory compliance, data quality or data completion in the DSMC monitoring report may lead to a recommendation by the DSMC Chair to the Winship Associate Director for Clinical Research to halt accrual or all research activities pending the development and implementation of a CAPA. The CAPA may include any or all of the following: suspension of accrual to the study; additional training for faculty and/or staff involved in the conduct of research; implementation of new procedures; improved procedures for data capture including completion of outstanding case report forms; or required modifications or amendments to the study. The PI will communicate the CAPA with timeline, in writing, to the DSMC Chair.

Following implementation of the CAPA, the DSMC will determine if it is appropriate to re-monitor the study to ensure that previously identified deficiencies have been adequately addressed. For cases in which accrual to the study or research activities have been suspended, the DSMC will review the PI’s response to determine if all items sufficiently address the committee’s concerns. The DSMC may accept the response and recommend trial continuation, in writing, to the PI and the Winship Associate Director for Clinical Research. If the PI’s response is deemed unacceptable or inadequate, the DSMC may request further action be taken to address and resolve significant issues prior to recommending trial continuation. The DSMC will communicate this further action request, in writing, to the PI and the Winship Associate Director for Clinical Research. Upon review of the DSMC recommendation, the Winship Associate Director for Clinical Research will decide if the trial may be re-opened or if suspension should continue. The Winship Associate Director for Clinical Research will communicate the decision in writing to the individuals and entities as previously mentioned above.

At Winship, early phase studies that involve dose escalations are usually conducted and reviewed by the Phase I Clinical Trials Working Group. For Phase I investigator-investigator studies that are conducted by other working groups, any decision regarding dose escalation will be reviewed and approved by the DSMC prior to implementation. The PI holds the responsibility to notify the DSMC in writing with the supportive data that justifies dose escalation/de-escalation. The committee will review the information provided by the PI and make recommendations for dose escalation or de-escalation.
2.5 Recommendations and Ratings

To summarize, upon review of the study, the DSMC will make one of the following recommendations:

- Study continuation as planned; no further action deemed necessary
- Study continuation with stipulations and/or protocol modifications
  - Stipulations and/or modification are expected to be formally addressed by the PI with a response provided to the DSMC within two weeks
- Study suspension with stipulations and/or protocol modifications
  - Stipulations and/or protocol modifications are expected to be formally addressed by the PI with a response provided to the DSMC prior to study resumption
- Study termination

In addition, the committee will assign an overall rating:

- Acceptable
- Acceptable, needs follow-up
- Unacceptable

2.6 Administrative Coordination

In addition to responsibilities mentioned in Section 2.3, a member of the monitor team or a designated administrative support staff provides further support by arranging committee meetings, creating the meeting agenda, and distributing meeting agenda, minutes and monitoring reports to committee members. All records, including database management, of DSMC activities are maintained by a member of the monitor team or a designated administrative support staff. The designee will draft the committee recommendation letter for review and approval by the DSMC Chair or Vice-Chair and distribute the approved letter to the study PI, along with other pertinent individuals. If the committee requests additional follow-up or response from the PI, a member of the monitor team or a designated administrative support staff will follow-up to ensure submission of requested documentation.

3.0 RISK-BASED MONITORING

3.1 Determining the Level of Risk

The extent of internal monitoring and DSMC review is variable depending upon the phase of the trial, trial type, the study sponsor, IND/IDE status, accrual rates, and follow-up status. The level of risk associated with each trial under the DSMC’s purview will be determined during CTRC review in conjunction with the protocol-specific monitoring plan approval by the DSMC. See Table 1 below for details of risk determination.

3.2 Frequency of Monitoring

A schedule will be prepared by the internal monitoring staff to ensure that trials under the DSMC’s purview are reviewed according to the DSMP or until the DSMC feels there are no subject safety concerns that require further monitoring. Once a study is scheduled/selected for monitoring (i.e., notification sent to PI and applicable study team members), deferment will not be allowed without the approval of the DSMC Chair or Vice-Chair. The DSMC, institution and regulatory authorities’ expectation is for study documentation, including data entry, to be maintained contemporaneously throughout trial conduct in a high-quality manner. Thus, the DSMC does not consider monitoring deferment acceptable. See Table 1 below for details of monitoring frequency for trials conducted at Winship sites.
<table>
<thead>
<tr>
<th>RISK LEVEL</th>
<th>EXAMPLES OF TRIAL TYPE</th>
<th>FREQUENCY OF INTERNAL MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>Phase I (toxicity/dose finding) or gene transfer therapeutic Investigator-Initiated study with institution or PI as IND/IDE holder (Emory faculty as sponsor) and not routinely monitored by a CRO</td>
<td>Every Six Months</td>
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<tr>
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<td>• Initial study monitoring will occur within 6 months from date of 1st subject accrued to study.</td>
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<td>• At that time, 2 of the 1st 5 subjects accrued will be monitored.</td>
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<td>• Thereafter, subsequent monitoring will occur in six month intervals if any subjects were accrued.</td>
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<td>• The population continuing to receive intervention will be monitored on a study-by-study basis.</td>
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<td>• At minimum, 10% of subjects accrued since previous monitoring will be reviewed.</td>
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<td>• An additional subject (or subjects) may be selected based on previously noted monitoring deficiencies or at DSMC discretion.</td>
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<td>• Continued monitoring will occur in six month intervals for the population continuing to receive intervention on a study-by-study basis.</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>• Non-therapeutic Investigator-Initiated study with IND/IDE (sponsor is Emory faculty)</td>
<td>Annual</td>
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<td></td>
<td>• Phase II interventional or therapeutic Investigator-Initiated study with IND/IDE (sponsor is Emory faculty)</td>
<td>• Initial study monitoring will occur within 1 year from date of 1st subject accrued to study.</td>
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<td>• Phase I/II Investigator-Initiated studies of FDA approved agents and other Phase II trials (i.e., commercially available agents or devices; IND Exempt or Nonsignificant Risk IDE)</td>
<td>• At that time, 2 of the 1st 5 subjects accrued will be monitored.</td>
</tr>
<tr>
<td></td>
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<td>• Thereafter, subsequent monitoring will occur in 1 year if any subjects were accrued. The population continuing to receive intervention will be monitored on a study-by-study basis.</td>
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<tr>
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<td>• At minimum, 10% of subjects accrued since previous monitoring will be reviewed.</td>
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<td>• An additional subject (or subjects) may be selected based on previously noted monitoring deficiencies or at DSMC discretion.</td>
</tr>
<tr>
<td>Low Risk</td>
<td>• Biomarker</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Non-interventional</td>
<td></td>
</tr>
</tbody>
</table>
3.3 Cooperative Group, NIH/NCI and Consortium Studies

The DSMC will review selected National Clinical Trial Network studies each year with equal representation of ECOG-ACRIN, NRG, and other group trials. NIH/NCI, consortium and institutional (non-Emory sponsored) studies also fall in this category of trials that are monitored according to Table 2 below. The studies with highest accrual during the preceding year and/or those that have experienced significant deficiencies in prior audits will be prioritized for review. The Winship Cancer Institute monitors assigned to the DSMC will verify informed consent, eligibility, data completion, accuracy and availability of source documentation as specified in this DSMP. These trials will be monitored if open to accrual. If a trial is closed to accrual, monitoring will be performed as deemed necessary by the DSMC. See Table 2 for further details regarding the monitoring frequency for trials conducted at Winship sites.

<table>
<thead>
<tr>
<th>EXAMPLES OF TRIAL TYPE</th>
<th>FREQUENCY OF INTERNAL MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsored (cooperative group, institutional*, consortium, NIH/NCI) Phase I, II, or III interventional trials (with or without IND/IDE) and not routinely monitored on-site by sponsor</td>
<td>Monitoring of prioritized trials will be based on rate of accrual as follows:</td>
</tr>
<tr>
<td><strong>Initial study monitoring will occur within 1 year from date of 1st subject accrued to study –</strong></td>
<td>If accrual at time of initial monitoring is ≤ 10, only 2 of the 1st 10 subjects accrued will be monitored. Thereafter, monitoring will not occur unless accrual reaches above 10 subjects. Once the 11th subject is accrued, monitoring will recommence within 1 year from the accrual date. At that time, at least 10% of subjects accrued since previous monitoring will be reviewed. Subsequent monitoring will occur as requested by sponsor, coordinating center, or at discretion of Winship DSMC. If accrual at time of initial monitoring is &gt; 10 but ≤ 20, 10% of subjects will be monitored at minimum. Thereafter, monitoring will not occur unless accrual reaches 30. Once the 30th subject is accrued, monitoring will recommence within 1 year from the accrual date. At that time, at least 10% of subjects accrued since previous monitoring will be reviewed. Subsequent monitoring will occur as requested by sponsor, coordinating center, or at discretion of Winship DSMC.</td>
</tr>
</tbody>
</table>

*institutional definition: represents study oversight is responsibility of investigator at another academic center

4.0 INTERNAL MONITORING

4.1 Overview

The DSMC is supported by full-time monitors and administrative support staff. The internal monitoring team is independent from any study protocol and does not perform any trial-related specific duties in order to uphold an unbiased approach to study monitoring. Oversight of the monitoring process and identification/assignment of studies for monitoring is provided by the Manager of the Internal Monitors. A qualified and trained individual will perform trial monitoring. The monitor will have appropriate experience to perform these duties. The monitor will be familiar with the investigational product(s), protocol, written informed consent, SOPs, GCP, and any other
applicable regulatory requirement(s). Monitors can ask the Associate Director for Clinical Research or the DSMC Chair (or a designee) for guidance and resolution of medical questions. Monitoring will be conducted according to the plan defined in the DSMP. These procedures shall assure that monitoring activities meet the FDA’s requirements as delineated in 21 CFR 50, 21 CFR 56, 21 CFR 812 for studies conducted under an IDE and 21 CFR 312 for studies conducted under an IND.

4.2 Responsibilities and Procedures

The DSMC will identify trials to be monitored at the time of initial CTRC approval. Once a trial is selected for monitoring, the assigned monitor will randomly select subject(s) for review based on parameters in Table 1 or 2 as noted above. Although the principal investigator and applicable study team members will receive notification of trial monitoring in advance, the subject selection will not be revealed in advance of the monitoring visit.

The DSMC monitors will review the protocol, amendments, informed consent documents, IRB submissions and meet with the principal investigator for clarification of study objectives. During the pre-monitoring meeting the PI, and any study team members in attendance, will be informed of items and subjects monitored for the DSMC review. The following may be reviewed:

- Appropriateness of informed consent documents and process documentation prior to performance of study-related procedures
- Inclusion/Exclusion criteria to ensure only eligible subjects are enrolled
- Review of data integrity
- Verification that the investigator and staff are performing trial functions in accordance with the approved protocol and any approved amendments
- Review of accuracy and timeliness of data collection and submission
- Verification of source documentation with case report forms focusing on study endpoints
- Tumor response evaluation: verification that responses are identified according to the protocol definition of response for any response that is a major study endpoint.
- Toxicity assessment
- Determination that AEs and SAEs are appropriately reported as required by GCP, the protocol, IRB policy, Winship SOPs and other regulatory requirements.
- Investigational product accountability and handling as specified in the protocol
- Treatment delivery or intervention per protocol
- Maintenance of essential regulatory documents
- Detect trends and/or system errors that may lead to non-compliance

Following the monitoring review/visit, the activities are described as follows:

- The monitor will provide a preliminary report of monitoring findings will be provided to the PI and other pertinent individuals involved in the conduct of the study, including the CRC/CRN and regulatory specialist.
- The PI is required to address and respond to all deficiencies noted in the preliminary monitoring report. The PI’s response(s) to deficiencies must be submitted within two weeks, although a more timely response may be required under certain circumstances. The PI should indicate any remaining deficiencies and provide a corrective action plan for resolution of deficiencies.
- The monitor will meet with the PI and, if available, the CRC/CRN to discuss the preliminary monitoring report deficiencies and responses prior to finalization of the monitoring report for DSMC review.
• The monitor will prepare a final monitoring summary report for the PI and DSMC. The final monitoring summary report should include:
  o Summary of systematic deficiencies
  o Significant protocol deviations
  o Summary of remaining deficiencies with proposed corrective and preventive action plan provided by PI
  o Recommendations for data collection, protocol revision for clarity
• Final DSMC review includes: the final monitoring summary report with corresponding PI response, CAPA submitted by the PI (if applicable), the PI’s summary of trial conduct to date, and available aggregate toxicity and safety data, including SAEs. The DSMC will render a recommendation and rating as outlined in Section 2.5 of the DSMP. In addition, the DSMC may elect to have the study re-monitored to ensure resolution of significant findings.
• The PI is responsible for ensuring that instances of egregious data insufficiencies that may impact the scientific integrity of the trial, evidence for unanticipated problems involving risk to subjects or others, or regulatory non-compliance, are reported to the IRB. Continuing Review submission to the IRB by assigned regulatory specialist will include DSMC recommendations.

See Appendix I for DSMC and internal monitoring process.

5.0 INTERACTIONS WITH THE FDA AND NCI

The Winship Associate Director for Clinical Research and the Director of the Clinical Trials Office are the primary contacts for the FDA and NCI for all trial-related activities. The sponsor is responsible for maintaining compliance with the IND/IDE regulations.

6.0 DSMP AND PRMS PURVIEW OVER CANCER-RELATED CLINICAL RESEARCH CONDUCTED AT WINSHIP CANCER INSTITUTE OF EMORY UNIVERSITY

All clinical research conducted at Emory University that involves interventions specifically targeted towards cancer patients or patient populations specifically identified as being at risk for cancer (Interventional Preventative and Interventional Diagnostic) will be entered into the Central Winship Cancer Institute Clinical Research database. All cancer-related clinical research studies will be reviewed by the CTRC as part of the PRMS of the Winship Cancer Institute and all interventional studies will be monitored by the DSMC as part of the DSMP of the Winship Cancer Institute. Faculty in all departments conducting interventional research conducted at Emory University will be responsible for ensuring that the studies are conducted in accord with FDA human subjects protections regulations 45 CFR 46, 21 CFR 50, 21 CFR 56, 21 CFR 312 for studies conducted under an IND and with 21 CFR 812 for studies conducted under an IDE.

7.0 AUDITS

7.1 External Audits Requested by the Winship Associate Director for Clinical Research

The Winship Associate Director for Clinical Research may request an external audit of a study by non-Winship or non-Emory faculty in exceptional circumstances, such as overwhelming conflict of interest by the members of the DSMC that would preclude sufficient members for an impartial review. If the Winship Associate Director for Clinical Research determines that an external audit of the study should be conducted, he/she will appoint external auditors (who may be members of the Emory faculty who are not involved with the study or outside, non-Emory experts) to conduct such an audit. The Winship Associate Director for Clinical Research will establish the scope and
7.2 Independent Audits

Audits beyond the scope of internal monitoring, as described in this document, can be done “For Cause” at the discretion of the DSMC. In the event that such an audit is required, a qualified independent auditor who may be a member of the Winship Cancer Institute, Emory faculty who are not involved with the study, or outside experts will be identified and engaged to conduct the audit. The report of such an independent audit will be delivered directly to the DSMC and reported to the IRB if appropriate.

8.0 DATA AND SAFETY MONITORING FOR INDIVIDUAL CLINICAL TRIALS

Every interventional clinical study at the Winship Cancer Institute must describe and implement a Data and Safety Monitoring Plan (DSMP). The plan may reference this document and should describe the frequency of monitoring and interim analyses, if any, that will be performed, including those to be performed by an outside entity. The DSMC will approve the DSMP for each clinical study that is conducted by a Winship Investigator with an IND/IDE. The DSMC may serve as the Data and Safety Monitoring Board (DSMB) for institutional trials that do not have an external DSMB. The DSMC offers assistance to investigators in establishing a DSMB for a given trial with members that have the necessary expertise. The membership for the individual DSMB consists of a subset of the DSMC members, and external experts whenever necessary. The PI for the study is provided with appropriate language for inclusion in their study protocol. See Appendix II for description of general elements necessary for a protocol specific DSMP.

9.0 MONITORING OF MULTI-SITE INVESTIGATOR-INITIATED TRIALS

The formation of the Multi-Site Program enables the Winship CTO to effectively provide oversight for the management of Winship faculty-sponsored trials conducted at participating institutions. The established multi-site SOPs ensure adequate monitoring of trial activities and conduct at participating institutions. The Multi-Site Coordinator (MSC) will carry out the monitoring activities in accordance with GCP, multi-site SOPs and the protocol specific monitoring plan. The Winship sponsor is responsible for assurance that the MSC is qualified to perform monitoring tasks through training and experience. Furthermore, the ultimate responsibility for overall subject safety as well as quality and integrity of the trial data lies with the Winship sponsor.

With the assistance of the Winship DSMC, additional oversight will ensure safeguards are in place for enhanced safety of study participants and considerations regarding validity of trial continuation. The DSMC will review external trial data, including but not limited to safety and toxicity data, for investigator-initiated protocols monitored by the committee. The sponsor will be required to submit a report on trial activities – local and participating sites, during the time of routine Emory site internal monitoring, separate from the monitoring performed by the MSC.

Following on-site monitoring at the participating institution by the MSC, a monitoring follow-up letter will be generated for submission to the sponsor as well as the participating site’s PI. The monitoring follow-up letter will also be provided to the Manager of the Internal Monitors for review. Should any serious or significant issues arise that indicate compliance problems or affect subject safety, the MSC’s monitoring report will be escalated for full DSMC review. For instances where local internal monitoring is no longer warranted but participating site monitoring continues, the trial data will be reviewed on a schedule that aligns with the on-site monitoring performed by the MSC. Specifically, the DSMC will review deviations and toxicity data, including SAEs, that occur at the participating institution.
APPENDIX I

DSMC Process

Unanticipated problems, related SAE, substantive protocol deviation, regulatory non-compliance reported immediately to DSMC and PI. PI is responsible for reporting to IRB.

Regular monitoring per DSMC

Internal Monitoring Process

Internal Monitoring Report

DSMC Review

No Significant Issues

DSMC recommends study proceed as planned

Significant Issues

GCP-Related Issues

Scientific-Related Issues

Re-monitoring following implementation of CAPA

Decline Suspension

DSMC recommends accrual suspension or study termination

PI

CTRC

IRB

Sponsor

Winship Director

Associate Director of Clinical Research concurs with DSMC recommendation

Notify

Notify

Notify

Notify

PI
APPENDIX II

GENERAL ELEMENTS OF DSMPs

- Oversight Responsibilities
  - Determining the necessity for a DSMB
  - Determining the DSMB sponsor

- Adverse Event Reporting
  - Description of adverse event determination/reporting procedures.
  - Proposed adverse event reporting schedules
  - Determination regarding who is to receive adverse event reports

- Data, Safety and Progress Reporting
  - Timetable for data submission
  - Monitoring and auditing timetable and description

- Study Closure – Safety and Efficacy/Futility Stopping Rules
  - Process for implementing study closure based upon significant risks, benefits, or study futility determination.
  - Procedures for unblinding/unmasking

- Privacy and Confidentiality
  - Methods described for ensuring clinical study privacy and confidentiality

- Principal Investigator Qualifications
  - Clear description of principal investigator qualifications to conduct the particular clinical study for which DSMP is being considered.

SPECIFIC DSMP REQUIREMENTS FOR INVESTIGATOR-INITIATED STUDIES

- Phase I and II Clinical Studies
  - The following necessary components of a DSMP are to be incorporated in the protocol:
    - The process for identifying and documenting UPs, AEs, SAEs and a description of appropriate reporting process as well as communication plan to other investigators
    - Correct and safe preparation and handling of all investigational agents
    - Procedures for investigational product accountability
    - Method for securing privacy and confidentiality
  - The following monitoring process requirements must be included in the DSMP:
    - Identification of monitoring oversight, and monitoring timetable.
    - Continuous monitoring of all study participants by the principal investigator
• Phase III Clinical Studies
  
  o Necessary components of DSMP to be incorporated in the protocol:
    - The process for identifying and documenting UPs, AEs, SAEs and a description of appropriate reporting process as well as communication plan to other investigators
    - Procedure for peer review of study endpoints
    - Method for securing privacy and confidentiality
    - A DSMB must be created or identified
    - The PI, the Study Statistician and internal monitors assigned to the DSMC will prepare a report for the DSMB every six months.
APPENDIX III

APPROVAL SIGNATURES

Kathleen Rodger, RN, BSN, MSHCM
Director, Clinical Trials Office
Winship Cancer Institute

Bassel El-Rayes, MD
Associate Director, Clinical Research
Winship Cancer Institute

Suresh Ramalingam, MD
Chair, Data and Safety Monitoring Committee
Winship Cancer Institute

1/20/2015
Date

1/20/2015
Date

1/20/2015
Date