

Abramson Cancer Center Data Safety and Monitoring Plan

Introduction

The Abramson Cancer Center (ACC) of the University of Pennsylvania places the highest priority on ensuring the safety of subjects participating in clinical trials. In response to the NIH/NCI policy request for all Cancer Centers to have plans regarding data and safety monitoring and auditing for cancer-related studies, we have taken a series of steps to improve both PI and institutional monitoring and auditing of clinical trials at the ACC. As part of the ACC Clinical Trials Scientific Review and Monitoring System, the ACC has established the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) which serves as a rigorous scientific peer review mechanism for all cancer protocols conducted within the University of Pennsylvania and the Data Safety and Monitoring Committee (DSMC) which is responsible for the overall quality control and quality assurance of all cancer related studies conducted within the University of Pennsylvania. The CTSRMC's focus is the scientific merit, priorities, and progress of Cancer Center clinical research while the DSMC's focus is data quality and subject safety monitoring and auditing. The guidelines governing both committees have been adapted from the NCI/NIH policies.

The organizational structure of the Abramson Cancer Center's Clinical Trials Scientific Review and Monitoring System has been revised, more clearly differentiating the scientific review process from the monitoring and auditing functions of the committees. The CTSRMC, Chaired by Doug Fraker, MD reviews all cancer related studies to provide rigorous scientific review of the protocols. The DSMC is Chaired by David Vaughn, MD. The Administrative Director of the CTSRMC and DSMC, Vicki Sallée, MS, RD provides oversight and management of the Committee's functions and serves as the Compliance Officer for the Cancer Center. Janine Koury serves as the CTSRMC coordinator and the DSMC Monitoring Specialist. The two Cancer Center committees provide a system for appropriate oversight and auditing of clinical research studies.

Institutional Data Safety and Monitoring Plan

The institutional DSMP provides guidance to all cancer center faculty and staff on the development and application of an effective study Monitoring Plan which serves as the quality assurance guidance document for the studies. Additionally, the DSMP details the Cancer Center wide practices and procedures concerning study and regulatory compliance.

The CTSRMC requires protocol submissions to include a Monitoring Plan (MP) that will be followed for the duration of the study by the investigative team. This plan should compliment any plans developed by study sponsors (where applicable) and must be via one of the templates developed by the DSMC. The purpose of a MP is to assure that each clinical study has a system for appropriate oversight and monitoring to ensure the safety of the participants and the validity and integrity of the data. The methods and degree of monitoring for clinical studies is commensurate with the type of study and level of risk. There are a number of options for monitoring trials depending upon the complexity, risks, and nature of the protocol. Monitoring exists on a continuum and can be as simple as the investigator submitting reports to the CTSRMC and the IRB or as complex as having a Data Safety Monitoring Board (DSMB). Other options include an independent individual/safety officer, a designated medical monitor, or an internal committee with explicit guidelines. Regardless of the method used, monitoring must be performed on a regular basis. The

development and implementation of the MP for a study is the responsibility of the study P.I., subject to review and approval by the DSMC and the CTSRMC.

Principles Used to Guide the Development of the ACC Institutional DSMP:

1. Protocols differ substantially in their levels and types of risk and no predetermined criteria can adequately meet the needs of all projects. The monitoring plan should be commensurate with the risks. The frequency of review, the parties responsible for review and the scope of review will all vary among studies. In general, the higher the risk, the more frequent and intensive the monitoring will need to be.

2. As the intensity of monitoring must be proportionate to risk, some effort must be made to characterize the risk. Factors that should be considered in assessing risk include: risk inherent to the population being studied, risk associated with the intervention or treatment, medication risk (i.e., approved drug for approved indication, approved drug for new indication, investigational agent not yet approved, study involves an IND, study is IND exempt, involves a medical device (IDE,) vulnerable populations being studied, complexity of the study (multi-dose, dose escalation, phase of study, investigator-initiated, multi-center), experience of research team, prior audit outcomes, oversight by other organizations, conflict of interest, and special circumstances. Table 1 summarizes levels of risk for monitoring purposes.

3. The amount of monitoring provided by a study sponsor, who may be NIH, NCI, CTEP, drug and medical device industries (pharmaceutical, biotechnology), impacts the amount of monitoring required by the study PI.

TABLE 1: Monitoring Risk Categories for Studies

Low Risk	Moderate Risk	High Risk*
<ul style="list-style-type: none"> • Study poses limited compared to that expected in daily life (blood draw, physical exam, psychological testing, residual collecting). • Behavioral Studies • Nutrition studies • Survey/Questionnaire Studies 	<ul style="list-style-type: none"> • Subjects treated with placebo for a recognized disease • Enrolls subjects with HIV/AIDS, hepatitis, or cancer on treatment protocols • Substantial risk (>5%) of a Serious Adverse Event originating from the underlying condition of the enrolled subject • Phase II clinical study • Phase I or II study with available safety data in humans • Post marketing study phase IV drug study or device (as defined by FDA). • Phase III, non investigator initiated 	<ul style="list-style-type: none"> • Involves an invasive procedure with significant risk • An investigator initiated IND trial • Implantation of device/agent with an IDE • Involves the use of a new chemical or drug for which there is little or no toxicology data in humans • A gene therapy study or research involving recombinant DNA molecules (gene transfer)[#] • Involves the manufacturing of agents on campus[#] • An investigator initiated

	<p>studies with an external sponsor (i.e. cooperative group study, industry sponsored trial</p>	<p>multi-center study⁺</p> <ul style="list-style-type: none"> • An investigator initiated randomized phase III clinical study⁺ • Study has provisions to waive consent in emergency circumstance
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*All high risk studies require a medical monitor or Safety Monitoring Committee.

⁺ Requires a Data Safety Monitoring Board.

[#] Requires a Safety Monitoring Committee

Monitoring Plan Requirements by Sponsor Type

- **NCI Cooperative Group Programs**

The ACC conducts clinical trials of the Eastern Cooperative Oncology Group (ECOG), the Radiation Therapy Oncology Group (RTOG), the Gynecological Oncology Group (GOG), the American College of Surgeons Oncology Group (ACOSOG), New Approaches to Brain Tumor Treatment (NABTT), American College of Radiology Imaging Network (ACRIN), National Bone Marrow Transplant Clinical Trials Network (NBMT-CTN), Cancer and Leukemia Group B (CALGB), National Surgical Adjuvant Breast Project (NSABP) and Children’s Oncology Group (COG).

Each national group conducts a range a therapeutic and non-therapeutic clinical trials. Because each group has appropriate monitoring plans in place to ensure patient safety and data quality, the CTSRMC only requires the PI to submit a monitoring plan template that will provide for trial oversight that compliments that of the cooperative group. The Cancer Center’s DSMC has developed a template that fulfills this requirement.

- **NCI/CTEP Sponsored Other NCI Contracts**

When an ACC principal investigator conducts a trial under funded by the NCI, each protocol must have specific plans for study monitoring, using established NCI data safety and monitoring systems. A matrix of reporting requirements and schedules is available at the CTEP website at <http://ctep.info.nih.gov>. Reporting requirements and times of reporting are dependent upon the phase of trial, grade of adverse event using Common Toxicity Criteria, attribution, and expectedness (see Appendix B, Tables 1 and 2). The PI must develop a comprehensive monitoring plan using the appropriate monitoring plan template that provides for complete quality assurance of the study. The Cancer Center’s DSMC has developed a template that fulfills this requirement.

- **Industry**

All clinical trials conceived and initiated by drug and/or medical device sponsors with subsequent Abramson Cancer Center participation will require a monitoring plan that will provide for trial oversight that compliments that of the study sponsor. These protocol specific plans will adhere to industry and FDA specified guidelines. The Cancer Center’s DSMC has developed a template that fulfills this requirement.

- **Local Investigator Initiated Studies**

Investigator-initiated studies, including many studies with NIH, NCI, or CTEP sponsorship, require particular attention for local monitoring and these studies receive the highest priority for local oversight. The PI must develop a comprehensive monitoring plan using the appropriate monitoring plan template that provides for complete quality assurance of the study. If the study is CTEP funded, the investigator must use the reporting requirements and schedules used by CTEP for handling adverse events and serious adverse events (Appendix B, Table 2). This plan must receive approval from the DSMC before the study can

receive full CTSRMC approval. Phase III studies are required to have a DSMB to ensure that there appropriate oversight of the clinical trial.

ACC Defined Essential Monitoring Plan Elements

In general, a MP should list who will be responsible for monitoring, the frequency of review, what aspects of the study will be inspected and must include a description of how adverse events will reported to the CTSRMC, the IRB and the other appropriate entities in accordance with current NIH, FDA, and/or local or state regulations. *DSMC and CTSRMC approved Monitoring Plan templates are provided in Appendix A.*

The MP should include the following:

1. Categorization of risk level (low, moderate, high).
2. Specify the IND holder
3. Explanation of how the study will be monitored, frequency of review, documentation of review.
4. Adverse events: If the study protocol does not detail how adverse events and serious adverse events are identified, assessed, recorded, and reported, these details must be included in the study specific Monitoring Plan. This includes the description, grading and attribution scales, outcome, identification of agencies who will receive adverse event reports (i.e., IRB, CTSRMC, GCRC, , FDA, OBA etc), the timing of the reports, how adverse events are to be monitored (i.e., via exams, vital signs, lab test, review of subjects medical chart, review of subjects diaries). Published forms such as AdEERS or MedWatch should be used in appropriate settings. (See Appendix B for suggested terms and definitions of adverse event information and reporting requirements).
5. A statement that all research project personnel have completed training in the protection of human research participants per guidelines issued by the U.S. Department of Health and Human Services, Office for Human Research Protections. Successful completion of the University of Pennsylvania's Patient Oriented Research training program fulfills this obligation.

Monitoring Plan Requirements for Clinical Trials Involving Agents Manufactured on Campus

Clinical trials that are conducted at the University of Pennsylvania with agents that are manufactured on campus are considered high risk and require close monitoring and compliance with GCP (Good Clinical Practice) and GMP (Good Manufacturing Practice). Examples of these types of clinical trials include dendritic cell vaccines, T-cell based therapy, etc. Trials such as these will require at least a Safety Monitoring Committee as well as personnel with expertise in GMP. The PI must develop a comprehensive monitoring plan using the appropriate monitoring plan template that provides for complete quality assurance of the study. This plan must receive approval from the DSMC before the study can receive full CTSRMC approval. (See Appendix E for further details). Investigators are referred to Vicki Sallée, Administrative Director of the DSMC at 215- 349-5238 or vsallee@mail.med.upenn.edu to further develop appropriate DSMP for these types of clinical trials.

Procedure for Submission of a Monitoring Plan to the CTSRMC

All protocols submitted to the CTSRMC must have a Monitoring Plan that is in compliance with the ACC's institutional Data Safety and Monitoring Plan. Following receipt of the

protocol, the CTSRMC Coordinator conducts an initial administrative review to ensure that a MP has been prepared and to ensure that all the requisite components of the protocol are present before forwarding the protocol to the DSMC Administrative Director for review and approval before the protocol is sent to the CTSRMC. The protocol will be returned to the investigator as incomplete if there is no MP. The CTSRMC will review and vote on the submitted protocol including an assessment of the MP. No protocol may receive full approval without approval of the MP. Investigators are encouraged to discuss proposed MP plans with Vicki Sallée, Administrative Director of the DSMC. A recommendation will be made concerning the plan as either adequate or requiring revision. If revision is requested, specific suggestions will be provided.

To facilitate implementation of this policy, two MP plan templates have been developed for investigators based on the sponsor type and are included in Appendix A of this document. These can be requested by contacting Vicki Sallée at 215-349-5238 or email: vsallee@mail.med.upenn.edu.

Responsibilities of the Principle Investigator (PI)

The PI is responsible for ensuring that the conduct of the study is in accordance with all applicable guidelines and regulations. Therefore, s/he must provide ongoing monitoring of data integrity which can be accomplished by: reviewing CRFs in a timely manner; open, timely and documented communication with the University's IRB, CTSRMC, DSMC, study sponsor and FDA (where applicable); ensuring source documentation for all CRF fields/questions; documentation of deviations from the study protocol; and maintaining all study files and documents in an orderly fashion in a regulatory binder. The PI must make sure that his/her clinical protocol has a structured adverse event determination description and clearly established reporting requirements. The PI must provide ongoing monitoring of data integrity. Patient safety will be monitored continuously by the P.I. by reviewing and documenting the participant's laboratory results and procedures in real time, identifying potential AEs, reviewing all AEs and SAEs for accuracy and completeness on an ongoing basis, reporting and documenting the reporting of AEs and SAEs to the IRB and the CTSRMC in accordance with sponsor's and all regulatory authority requirements. The approved study Monitoring Plan will serve as the guidance document that will allow the PI and his/her study team to accomplish all of these requirements throughout the duration of the study.

- **Information that should be submitted to CTSRMC and/or DSMC**
 - All early termination/suspension of trials will be immediately reported to the CTSRMC regardless of cause. The DSMC will be immediately notified of trials terminated/suspended due to safety issues.
 - All protocol violations/deviations should be immediately reported to the CTSRMC.
 - All amendments to study protocols and informed consent forms must be submitted to the CTSRMC for approval prior to implementation of the changes. The amendments will be reviewed on an expedited basis (where appropriate) by the CTSRMC.
 - All SAEs must be reported to the DSMC in accordance with all applicable regulations and guidelines. All SAE reports will be reviewed by the DSMC during the monthly meeting.
 - Annual progress reports must be sent to the CTSRMC with a summary of adverse events. The annual progress report (continuing review) that is submitted to the IRB can serve as the annual report. Any additional

information learned by the PI that might impact on the safety and well being of subjects should be included in the annual progress report.

Responsibilities of the Data Safety and Monitoring Committee (DSMC)

The DSMC meets monthly and focuses on data monitoring and patient safety issues, protocol deviations, adverse events and serious adverse events, audit planning, and review of accrual. Audit reports, which detail the findings of ongoing audits, are reviewed at the monthly meetings of the DSMC. The DSMC also reviews reports generated by internal or external DSMBs.

All clinical trials approved by the CTSRMC are audited by the DSMC based on the risk assigned to the clinical study. The purpose of these audits is to assure protocol compliance, data integrity and to ensure that cancer clinical trials are conducted in accordance with federal, state, and institutional regulations. Areas reviewed include consent and regulatory procedures, accrual rates, eligibility criteria, treatment administration, reporting of adverse events, response assessment, patient follow up, data completeness, and adherence to ICH guidelines for Good Clinical Practice (GCP). The DSMC has the authority to suspend or terminate a trial for any patient safety concerns and/or major audit deficiencies. See Appendix D for details regarding the auditing function of DSMC.

Auditing Timelines

The extent of DSMC monitoring/auditing is dependent upon many factors including the trial sponsor and risk.

- **NCI Cooperative Groups**

The DSMC randomly selects cooperative group trials for auditing. The random selection will allow for a sampling across groups and disease sites. Additionally, the DSMC requires the PI to provide a copy of all inspection reports conducted by the respective group to the committee for review. All SAEs on subjects enrolled on these studies must be reported to the DSMC for review. Based on local or national/external SAEs reported, the DSMC has the authority to close any active study to further local accrual and/or require more detailed reporting of SAEs observed and a description of steps taken to minimize patient risk and maximize the safety of subjects.

- **NCI/CTEP Sponsored Other NCI Contracts**

These studies are audited by the DSMC based on the risk level assigned by the CTSRMC. All SAEs on subjects enrolled on the study must be reported to the DSMC. Based on local or national/external SAEs reported, the DSMC has the authority to close any active study to further local accrual and/or require more detailed reporting of SAEs observed and a description of steps taken to minimize patient risk and maximize the safety of subjects.

- **Pharmaceutical/Biotechnical Industry**

The DSMC randomly selects industry sponsored trials for auditing. The random selection will allow for a sampling across sponsors and disease sites. Additionally, the DSMC requires the PI to provide a copy of all inspection reports conducted by the sponsor to the committee. All SAEs on subjects enrolled on these studies must be reported to the DSMC for review. Based on local or national/external SAEs reported, the DSMC has the authority to close any active study to further local accrual and/or require more detailed reporting of

SAEs observed and a description of steps taken to minimize patient risk and maximize the safety of subjects.

- **Investigator Initiated Studies**

These studies are audited by the DSMC as required by the risk level assigned by the CTSRMC. All SAEs on subjects enrolled on the study must be reported to the DSMC. Based on SAEs reported, the DSMC has the authority to close any active study to further accrual and/or require more detailed reporting of SAEs observed and a description of steps taken to minimize patient risk and maximize the safety of subjects. In addition to DSMC auditing, the CTSRMC may request that the DSMC provide a real-time study monitor for certain high risk in-house studies. In this case, the DSMC Administrative Director will meet with the study PI to establish a plan which will define the frequency and intensity of DSMC monitoring. The areas including in the plan will be inspection intervals, study aspects, regulatory documents and agent accountability (where applicable). The DSMC monitor will make on-going suggestions to the PI for study improvement which may require changes to established processes to ensure continued subject safety and collection of high quality data.

Audit Criteria and Procedures

Audits are conducted by Janine Koury, Vicki Sallée and Dr. Vaughn. Areas addressed in these audits include consent and regulatory procedures, eligibility criteria, treatment administration, reporting of adverse events, response assessment, patient follow-up, adherence to IRB policy and overall quality of data. The auditors compare source documentation to the study forms used to collect study data. All discrepancies, omissions or queries are recorded on the audit forms. Treatment administration is also verified. All IRB and CTSRMC approvals (initial and annual), adverse event reporting, drug accountability and miscellaneous IRB correspondence are reviewed as well.

All non high risk protocols are audited six months from their first subject accrual and annually thereafter. High risk protocols are audited six months from their first subject accrual and every six month thereafter. However, this schedule may be changed at the discretion of the CTSRMC. Priority of review is given to in-house studies and non-cooperative NIH/NCI funded studies since most industry and cooperative group sponsored trials are audited on a regular basis by the sponsor. However, the DSMC audits industry and cooperative studies as part of a random selection process. Investigators are notified in advance of the selection of their protocol for review and cases are randomly selected. Three randomly selected patients or 10% of the total accrual, whichever is higher, are audited. A formal report is written to the PI within one week of the audit. The committee may alter the frequency of re-monitoring based on the audit findings and degree of deficiencies. If an audit is unacceptable due to major deficiencies, the DSMC Chair and the Administrative Director meet with the PI to discuss the findings of the audit and necessary corrective actions. If the deficiencies involve patient safety or serious regulatory violations, the Cancer Center Director, DSMC Chair, and DSMC Administrative Director will meet to discuss necessary actions concerning study status.

Additional Monitoring Required by the ACC Institutional Data Safety and Monitoring Plan

Medical Monitor

The Medical Monitor will be a physician who is not directly involved in the trial and is not collaborating with the sponsor/investigator in any other trial. In the role, s/he will review all AEs including grading, toxicity assignments, all other safety data and activity data observed in the ongoing clinical trial along with discussing relevant animal and toxicology studies and

similar investigational agents. The Medical Monitor may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial. All clinical investigator-initiated trials considered high risk will require at least a Medical Monitor and may be necessary for certain moderate risk studies as well.

Safety Monitoring Committee (SMC)

A SMC is composed of 2-3 members who have the qualifications and expertise to monitor the clinical study. Members must not be affiliated with the study. The committee will meet on a regular basis (frequency dependent on details of the clinical study) to review the conduct of the study and all adverse events. The primary responsibility of the SMC is to monitor participant safety. The structure and operating procedures for a SMC is less formal than a DSMB.

Data and Safety Monitoring Board (DSMB)

NIH requires all Investigator-Initiated Phase III randomized clinical trials to have a DSMB. Currently there are no requirements for any other type of trials; however, the investigator may organize a DSMB if they feel it is necessary. The CTSRMC also reserves the right to recommend a DSMB where it believes necessary. Table 1 provides examples of clinical studies in which a DSMB is required. If an independent DSMB is required for adequate subject safety, the frequency of DSMB meetings should be provided as well as a proposed list of data items to be provided to the DSMB. Depending upon the specifics of the clinical trial, DSMB members may be internal or external. If possible, the P.I. should nominate prospective DSMB members (including a curriculum vitae or biosketch). Members of a DSMB must disclose any potential conflicts of interest to the trial P.I. Conflict of interest can include professional interest, proprietary interest, or miscellaneous interest in accordance with University of Pennsylvania Conflict of Interest Policy as well as the NIH Grants Policy Statement. All protocols required to have a DSMB must submit a DSMB proposal along with the study protocol to the CTSRMC prior to approval. See Appendix C for further information regarding the development of a DSMB.

University of Pennsylvania Patient Oriented Research Training/Certification

The University of Pennsylvania has established and implemented a Research Orientation program in compliance with the NIH requirements for all personnel involved in the design and conduct of research involving human subjects. The program is a two level web-based training and certification program that includes video training and testing on federal regulations, University of Pennsylvania policies and procedures applicable to human subject research, the ethical use of human subjects in research and conflict of interest. All staff directly involved in research of human subjects (i.e. PI and study specific personnel) is required to take this certification program and pass the test that is provided at the end of each training module. The CTSRMC has access to the University's POR training database and thus can ensure that cancer center research staff has successfully completed the required training.

University of Pennsylvania Institutional Review Board (IRB)

The University of Pennsylvania IRB reviews all research involving human subjects at the University of Pennsylvania. The IRB ensures that research meets ethical standards and is conducted according to federal, state and local regulations. No cancer related clinical protocol can receive full approval from the IRB without CTSRMC approval. As part of the annual review process, the IRB examines trials for accrual and reviews study progress.

The IRB reviews SAE reports as they are received and reviews aggregate adverse event reports annually.

Office of Human Research

The Office of Human Research (OHR) is an entity in the University of Pennsylvania School of Medicine which seeks to promote human research for the advancement of healthcare while ensuring the highest level of research participant safety and facilitating the highest quality research within the University by:

- Realizing the best research standards through adherence to University and government research policies and regulations
- Supporting investigators and research teams through process improvement, innovative technologies, and education and training initiatives
- Propagating best operational practices to maximize the efficiencies of research activities
- Collaborating with University organizations involved with human research

Further Guidance

In developing a study Monitoring Plan, refer to the following sources. National Institutes of Health Policy for Data Safety and Monitoring dated June 10, 1998

(<http://grants.nih.gov/grants/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 issued a policy on June 22, 1999 for the data and safety monitoring of all trials with special emphasis on randomized phase III trials by Data Safety and Monitoring Boards (DSMBs) (<http://deainfo.nci.nih.gov/grantpoliceis/datasafety.htm>). The NCI published the essential elements of a DSMP on April 1, 2001, (<http://cancertrials.nci.nih.gov/researchers/dsm/html/essential.html>).

FDA:

<http://www.fda.gov/oc/oha>

Safety monitoring guidelines.

(<http://www.nih.gov/niams/clinical/dsmb3.html#>)

If you need additional assistance or have questions concerning this guidance document, please contact:

Vicki Sallée, MS, RD

Administrative Director, CTSRMC and DSMC

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**APPENDIX A
Template Monitoring Plans**

MONITORING PLAN FOR IN-HOUSE TRIALS

**UPCC Number
Title of Protocol
Principal Investigator
Sponsor**

PURPOSE:

Principal Investigators acting as study sponsors are responsible for monitoring the safety of participants and verifying the validity and integrity of study data on an on-going basis for the study duration. This Monitoring Plan serves as documentation of the all the levels of monitoring that will be conducted during for this trial.

RISK OF STUDY:

- Minimal
- Low
- Moderate
- High

ADDITIONAL MONITORING ENTITIES:

- Cancer Center's **real time monitoring service as required by the CTSRMC (www.CTSRMC.org)**

Monitored every _____ days

List items that will be monitored (e.g. CRFs, Clinic Charts, Drug Accountability etc.)

- Medical Monitor

Provide the frequency of monitoring, items that will be reviewed, details about the monitor and his/her authority in regards to the study.

- Safety Monitoring Committee (SMC)

Provide the frequency of monitoring, items that will be reviewed, details about the committee membership and its authority in regards to the study.

Data Safety Monitoring Board (DSMB)

Provide the frequency of monitoring, items that will be reviewed, details about the board and its authority in regards to the study.

Note: This study may also be audited by Data and Safety Monitoring Committee in accordance with the UPCC Policy and Procedure for Auditing Clinical Protocols.

EVALUATING ADVERSE EVENTS:

During the course of the study, safety will be monitored on an ongoing basis by the Investigator(s) and the Research Coordinator. The Investigator(s) will review the study charts

to evaluate Adverse Events (AEs) every _____ day(s) and determine the grade, relationship to the study agent/device/procedure and decide the course of action for the participant(s). All Adverse and Serious Adverse Events will be documented on an Adverse Event CRF.

Adverse Events are defined as- Any unfavorable and unintended sign (including abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

Serious Adverse Events are defined as- fatal, or life-threatening (real risk of dying), or requires hospitalization / prolongs hospitalization, or persistent or significant disability/incapacity, or results in a birth defect or congenital anomaly, or is cancer-causing. All hospitalizations (or prolongation of existing hospitalization) for medical events regardless of phase of study, expected or unexpected attributions are considered SAEs with the exception of planned procedures. Other kinds of events can be labeled “serious adverse events” at the discretion of the investigator.

SAE exceptions for this study are detailed below:

MONITORING PLAN FOR IN-HOUSE TRIALS

**UPCC Number
Title of Protocol
Principal Investigator
Sponsor**

GRADING ADVERSE EVENTS

AEs will be graded according to _____ (e.g. Common Toxicity Criteria 3.0). For events not included in the tool identified above, the following will be used:

Mild: Noticeable to the subject, does not interfere with the subject’s daily activities, usually does not require additional therapy, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject’s daily activities, possibly requires additional therapy, but does not require discontinuation of the study.

Severe: Severely limits the subject’s daily activities and may require discontinuation of the study. This would include all adverse events defined as “serious adverse events”.

Grading exceptions for this study are detailed below:

DETERMINING EXPECTEDNESS:

Unexpected Adverse Event: Any adverse event that is not consistent with known, previously observed reactions. An unexpected adverse event varies in nature; intensity or frequency from information in the investigational drug/agent provided in the Investigator’s Brochure, package insert or safety reports, the clinical protocol, or the consent form.

Expected (known) Adverse Event: An adverse event, which is included in the labeling, package insert, Investigator’s Brochure or the NCI agent specific Expected Adverse Event List.

DETERMINING ATTRIBUTION:

An assessment of the relationship between the adverse event and the drug/intervention will be made for each occurrence by the Principal Investigator.

Definitely related: An adverse event has a timely relationship to the administration of the investigational drug/study procedure and follows a known pattern of response for which no alternative cause is present.

Probably related: An adverse event that has a timely relationship to the administration of the investigational drug/study procedure and follows a known pattern of response but for which a potential alternative cause may be present.

Possibly related: An adverse event that has a timely relationship to the administration of the investigational drug/study procedure and follows no known pattern of response, but for which a potential alternative cause does not exist.

Unrelated: There is evidence that the adverse event is definitely related to a cause other than the investigational drug/study procedure; in general, no timely relationship to the administration of the drug/procedure exists, or if so, the event does not follow a pattern of response and an alternative cause is present.

SAE REPORTING:

SAEs will be reported to the following:

- FDA
Timeline for reporting _____
Method(s) of reporting _____
- NCI/NIH
Timeline for reporting _____
Method(s) of reporting _____
- IRB
Timeline for reporting _____
Method(s) of reporting _____
- CTSRMC
Timeline for reporting _____
Method(s) of reporting _____
- Medical Monitor
Timeline for reporting _____
Method(s) of reporting _____
- Safety Monitoring Committee (SMC)
Timeline for reporting _____
Method(s) of reporting _____
- Data Safety Monitoring Board (DSMB)
Timeline for reporting _____
Method(s) of reporting _____

MONITORING DATA QUALITY

The study team is responsible for collecting and recording all clinical data required by the protocol. This includes ensuring that all source documents exist for the data on the case report forms, data fields are completed appropriately and all corrections are done according to Good Clinical Practice (GCP). Designated members of the study team will review the CRFs and corresponding source documents every _____ days. The Designees for this study are _____.

Any inconsistencies will be corrected in a timely manner and reviewed again by the designees in _____ days.

Protocol deviations identified during the review will be reported to the following:

- FDA
- NCI/NIH
- IRB
- CTSRMC
- Medical Monitor
- Safety Monitoring Committee
- Data Safety Monitoring Board (DSMB)

Lab results for each patient will be reviewed on an **ongoing basis** and the review will be documented by initialing and dating the lab report(s). Also, all study procedures (e.g. X-ray, CT, MRI, Ultrasound, Mammograms) will be reviewed in a timely manner by the PI(s).

MONITORING AGENT/DRUG/DEVICE ADMINISTRATION AND ACCOUNTABILITY

All agents identified in the protocol as being required will be documented in the study charts. The PI will review study agent/drug administration records every _____ days. Any inconsistencies identified will be addressed within _____ days and where appropriate, reported as deviations to the entities identified above.

EVIDENCE OF TRAINING IN HUMAN SUBJECT RESEARCH

All members of the study team have completed the University of Pennsylvania's Patient Oriented Research (POR) Training Program.

Note: NIH patient oriented research training is no longer accepted as a replacement for POR training by the School of Medicine.

PI's Signature

Date

APPENDIX A Template Monitoring Plans

PI MONITORING PLAN FOR SPONSORED TRIALS

UPCC Number
Title of Protocol
Principal Investigator
Sponsor

PURPOSE:

Principal Investigators are responsible for monitoring the safety of participants and verifying the validity and integrity of study data on an on-going basis regardless of monitoring by external groups/organizations. This Monitoring Plan serves as documentation of the PIs plans for monitoring his/her study and must be completed for **every** study in addition to the plans developed by a sponsor/cooperative group.

RISK OF STUDY:

- Minimal
- Low
- Moderate
- High

IN ADDITION TO THE PI, WHO ELSE WILL MONITOR THIS STUDY? (check all that apply)

- External group (i.e., pharmaceutical sponsor, contract research organization, CRO)
- NCI Sponsored Cooperative Group
- Cancer Center's **real time monitoring service as required by the CTSRMC (www.CTSRMC.org)**
- Medical Monitor
- Safety Monitoring Committee (SMC)
- Data Safety Monitoring Board (DSMB)

Note: The corresponding study protocol must provided details regarding how monitoring will be performed, the frequency of monitoring and items that will be reviewed. Additionally, for studies using a Medical Monitor, SMC or DSMB, the corresponding study protocol must contain details about the selection of members and authority of the committee.

This study may also be audited by Data and Safety Monitoring Committee in accordance with the UPCC Policy and Procedure for Auditing Clinical Protocols.

HOW WILL MONITORING BE PERFORMED?

During the course of the study, safety and data quality will be monitored on an ongoing basis by the Investigator(s) and the Research Coordinator. The Investigator(s) will review the study charts

to evaluate Adverse Events (AEs) every _____ day(s) and determine the grade, relationship to the study agent/device/procedure and decide the course of action for the participant(s). AEs will be graded according to _____ (e.g. Common Toxicity Criteria 3.0). Section(s) _____ of the study protocol defines adverse and serious adverse events including grading and expectedness.

The PI is responsible for ensuring timely reporting of SAEs to all applicable agencies/offices.

PI MONITORING PLAN FOR SPONSORED TRIALS

**UPCC Number
Title of Protocol
Principal Investigator
Sponsor**

SAEs will be reported to: **(check all that apply)**

- Sponsor
- CRO
- FDA
- NCI/NIH
- IRB
- CTSRMC
- Medical Monitor
- Safety Monitoring Committee (SMC)
- Data Safety Monitoring Board (DSMB)

Note: The corresponding study protocol must define serious adverse event reporting for this study.

The study team is responsible for collecting and recording all clinical data required by the protocol. This includes ensuring that all source documents exist for the data on the case report forms, data fields are completed appropriately and all corrections are done according to Good Clinical Practice (GCP). Designated members of the study team will review the CRFs and corresponding source documents every _____ days. The Designees for this study are _____.

Any inconsistencies will be corrected in a timely manner and reviewed again by the designees in _____ days.

Protocol deviations identified during the review will be reported to: **(check all that apply)**

- Sponsor
- CRO
- FDA
- NCI/NIH
- IRB
- CTSRMC
- Medical Monitor
- Safety Monitoring Committee
- Data Safety Monitoring Board (DSMB)

The PI(s) will review lab results for each patient on an **ongoing basis** and will document the review by initialing and dating the lab report(s). Also, all study procedures (e.g. X-ray, CT, MRI, Ultrasound, Mammograms) will be reviewed in a timely manner by the PI(s).

EVIDENCE OF TRAINING IN HUMAN SUBJECT RESEARCH

- All members of the study team have completed the University of Pennsylvania’s Patient Oriented Research (POR) Training Program.

Note: NIH patient oriented research training is no longer accepted as a replacement for POR training by the School of Medicine.

PI’s Signature

Date

APPENDIX B

Definitions, Terminology, and Reporting Requirements of Adverse Events: Tools for Clinical Investigators

The following definitions are similar to those used in monitoring of Investigational New Drug (IND) trials by the FDA and by the NCI. You may consider using these definitions for the CTSRMC Data Safety Monitoring Plan if you have no other definitions to follow for your study.

1. Basic Terms

A. Adverse Event

Any unfavorable and unintended sign (including abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

B. Serious Adverse Event

During clinical investigations, adverse events may occur which may be significant enough to lead to important changes in the way a drug or device is used. This is especially true for reactions which in their most severe forms, threaten life or function. Therefore, special medical or administrative criteria are needed to define reactions either due to their nature (“serious”) or due to the significant, unexpected, information they provide, and therefore justify expedited (rapid) reporting. The purpose of expedited reporting is to make regulators, investigators, and others, aware of new, important information on serious reactions.

A Serious Adverse Event (SAE) is defined any of the following: fatal, or life-threatening (real risk of dying), or requires hospitalization / prolongs hospitalization, or persistent or significant disability/incapacity, or results in a birth defect or congenital anomaly, or is cancer-causing. All hospitalizations (or prolongation of existing hospitalization) for medical events regardless of phase of study, expected or unexpected attributions are considered SAEs.

Other kinds of events can be labeled “serious adverse events” at the discretion of the investigator.

2. Severity Grading Scale for Adverse Events

Many disease specific groups have developed toxicity grading scales. For example, most cancer clinical trials use the CTC, Common Toxicity Criteria, developed by the NCI. The CTC provides a descriptive terminology which is utilized for adverse event reporting. A grading (severity) scale is provided for each adverse event term (<http://ctep.info.nih.gov>). If no guidelines exist, then the following scale can be used:

Mild: Noticeable to the subject, does not interfere with the subject’s daily activities, usually does not require additional therapy, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject’s daily activities, possibly requires additional therapy, but does not require discontinuation of the study.

Severe: Severely limits the subject's daily activities and may require discontinuation of the study. This would include all adverse events defined as "serious adverse events".

3. **Expectedness of an Adverse Event**

Adverse events can involve previously unobserved or undocumented reactions, so called "unexpected", or can be "expected".

Unexpected Adverse Event: Any adverse event that is not consistent with known, previously observed reactions. An unexpected adverse event varies in nature; intensity or frequency from information in the investigational drug/agent provided in the Investigator's Brochure, package insert or safety reports, the clinical protocol, or the consent form.

Expected (known) adverse event: An adverse event, which has been reported in the Investigator's Brochure, the clinical protocol, consent form or is listed in the NCI agent specific Expected Adverse Event List which can be obtained at the CTEP web site.

4. **Attribution/Association with the Drug or Intervention:**

An assessment of the relationship between the adverse event and the drug/intervention will be made for each occurrence by the Principal Investigator.

Definitely related: an adverse event has a timely relationship to the administration of the investigational drug/study procedure and follows a known pattern of response for which no alternative cause is present.

Probably related: an adverse event has a timely relationship to the administration of the investigational drug/study procedure and follows a known pattern of response, but for which a potential alternative cause may be present.

Possibly related: an adverse event has a timely relationship to the administration of the investigational drug/study procedure and follows no known pattern of response, but a potential alternative cause does not exist.

Unrelated: there is evidence that the adverse event is definitely related to a cause other than the investigational drug/study procedure; in general, no timely relationship to the administration of the drug/procedure exists, or if so, the event does not follow a pattern of response and an alternative cause is present.

5. **Assessing an Adverse Event**

Adverse event identification and reporting is a routine part of every clinical trial. The first step is to identify the adverse event. For studies conducted at the UPCC, the NCI Common Toxicity Criteria (CTC) will generally be used. The CTC term is then applied and the severity of the AE graded using the CTC criteria (or other appropriate grading system). Next, determine if the adverse event is related to the medical treatment or procedure (attribution). If so, determine whether the adverse event is expected or unexpected. With this information and the adverse event section of each protocol, the investigator can determine whether an adverse event should be reported as an expedited report (very rapid reporting) or a routine report. The NCI has developed specific requirements for adverse event reporting requirements, based upon guidelines developed by the FDA and DHHS which are summarized in the tables below and can be found at the CTEP home page: <http://ctep.info.nih.gov>.

6. Expedited Adverse Event Reporting Requirements

The reporting requirements and timing of reporting are dependent on the phase of trial (1,2,3), grade (severity), attribution and whether the event is expected or unexpected. The NCI has specific requirements for expedited reporting of adverse events <http://ctep.info.nih.gov>. Table 1 and 2 below. In general, expedited reporting is required for all SAEs, and grade 4 and 5 adverse events, and some grade 3 adverse events depending upon whether the AE is expected or unexpected. Expedited reporting generally requires a report by phone to the IRB and sponsor (i.e. FDA, NIH, pharmaceutical company, CRO), as soon as possible, but no later than 7 calendar days after first knowledge, followed by a written report within 10-15 days. For studies conducted with the NCI, the AdEERS system should be used for expedited reporting of adverse events. The CTSRMC must also notified in writing of any expedited adverse events reported.

Table 1. NCI Adverse Even Reporting for Local, Investigator-Initiated Phase I Trials

UNEXPECTED EVENT		EXPECTED EVENT	
Grades 2-3 Attribution of Possible, Probable or Definite	Grades 4 and 5 Regardless of Attribution	Grades 1-3	Grades 4 and 5 Regardless of Attribution
<p>Grade 2 – Expedited report to within 10 working days</p> <p>Grade 3 – Report by phone/fax within 24 hrs. Expedited report to follow within 10 working days.</p> <p>Grade 1 – adverse event reporting not required.</p>	<p>Report by phone within 24 hrs. Expedited report to follow within 10 working days.</p> <p>NOTE: this includes deaths within 30 days of the last dose of treatment.</p>	<p>Adverse Event Expedited Reporting is NOT required.</p>	<p>Report by phone within 24 hrs. Expedited report to follow within 10 working days.</p> <p>NOTE: This includes deaths within 30 days of the last dose of treatment.</p>

Table 2. NCI Adverse Even Reporting for Local, Investigator-Initiated Phase II – III Trials

UNEXPECTED EVENT		EXPECTED EVENT	
Grade 3 Attribution of Possible, Probable or Definite	Grades 4 and 5 Regardless of Attribution	Grades 1-3	Grades 4 and 5 Regardless of Attribution
<p>Expedited report within 10 working days.</p>	<p>Report by phone by within 24 hrs. Expedited report to follow within 10 working days.</p> <p>NOTE: This includes deaths within 30 days of the last dose of treatment.</p> <p>Any late death attributed to the agent</p>	<p>Adverse Event expedited Reporting is NOT required.</p>	<p>Expedited report, including Grade 5 Aplasia in leukemia patients, within 10 working days.</p> <p>NOTE: This includes deaths within 30 days of the last dose of treatment.</p> <p>Any late death attributed to the agent</p>

	should be reported within 10 working days.		should be reported within 10 working days.
--	--------------------------------------------	--	--------------------------------------------

Depending upon the clinical protocol and the sponsor, for commercial agents (drugs not provided under an IND and obtained from a commercial source) the FDA requires expedited reporting of unexpected and serious (not listed in the package insert, life threatening (grade 4), or unexpected, fatal (grade 5) events with an attribution of possible, probable, or definite. These events should be reported within ten (10) working days. These adverse events with commercial agents must be reported to the FDA using the MedWatch Form. A copy of the MedWatch form can be obtained from the FDA’s MedWatch Web site www.fda/medwatch . The MedWatch form can be sent the following online, by mail or fax. MedWatch 5600 Fishers Lane Rockville, Maryland 20852-9787. Fax at 1-800-332-0178.

It is critically important that the clinical protocol and MP indicate what to report, when to report and where to report adverse events and serious adverse events (i.e. IRB, GCRC, CTSRMC, NCI, FDA, OBA).

Trials for which the NCI is the IND sponsor have somewhat different reporting requirements in addition to those above: <http://ctep.info.nih.gov/handbook/handbook/HandBookIEPF.htm>)

Investigations involving recombinant DNA molecules have additional reporting requirements in addition to those above(<http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html>).

Note: Annual AE summary reports and expedited AE reports should not have patient identifiable material in them. Each report should be identified by a study ID number or some other identifying number that can be used by the investigator to identify the patient.

APPENDIX C

Guidelines Regarding Data Safety Monitoring Board (DSMB)

DSMB membership

- A DSMB will consist of no fewer than 3 members. At a minimum, the DSMB should be composed of at least one physician with appropriate medical and scientific expertise and a biostatistician. DSMB members may include investigators outside of the University of Pennsylvania. For some studies there may be a requirement for external members.
- Data Safety Monitoring Board (DSMB) members should not be involved in the study and should not have a conflict of interest.
- A curriculum or biosketch must accompany the nomination of a DSMB member. It is the responsibility of the P.I. to constitute the membership of the DSMB. The CTSRMC reserves the right to appoint additional members to a DSMB to include scientific expertise in topic areas relevant to the trial such as biostatistics, ethics, or patient advocacy.
- Like investigators, DSMB members are subject to the University of Pennsylvania's policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies.

DSMB Responsibilities

The DSMB must meet on a regular schedule (not less than twice a year) over the course of study (with additional meetings as needed).

- Review data (including blinded data) over the course of the trial relating to efficacy, recruitment, randomization, compliance, retention, protocol adherence, trials operating procedures, form completion, intervention effects, gender and minority inclusion and subject safety.
- Identify problems relating to safety over the course of the study. Inform study principal investigator via written report, who in turn will ensure that all clinical collaborative site principal investigators receive this report.
- Review major proposed modifications (amendments) to the study prior to their implementation (i.e., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Identify needs for additional data relevant to safety issues and request these data from the study investigators.
- Propose appropriate analyses and periodically review developing data on safety and endpoints.
- At each meeting, consider the rationale for continuation of the study, with respect to recruitment, progress of randomization, retention, protocol adherence and compliance, data management, safety issues, and outcome data, if relevant, and make a recommendation for or against continuation of the trial.

- Provide the principal investigator and CTSRMC with written reports following each DSMB meeting. The principal investigator will then forward the report to the IRB and other relevant committees and agencies.
- Provide advice on issues regarding data discrepancies found by the data auditing system or other sources. If the CTSRMC requests this advice, it should be provided by the DSMB in writing within one month of the date of the request.
- If there is more than one clinical site, the study principal investigator is responsible for sending the reports to individual site principal investigators, who in turn are required to distribute the report to their local IRBs, as detailed in the NIH “Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-supported Multicenter Clinical Trials” (NIH Guide for Grants and contracts, June 11, 1999).

DSMB Meetings

DSMB meetings will be divided into three parts. First is an open session during which members of the clinical trial team may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the DSMB. Issues discussed may include accrual, protocol compliance, and general toxicity. Outcome results must not be discussed during the open session. Following the open session, a closed session involving the DSMB, and study statistical staff will be held. The statistician(s) should present and discuss the outcome results with DSMB. A final executive session involving only DSMB members should be held to allow the DSMB opportunity to discuss the general conduct of the trial and all outcome results, including toxicities and adverse events, develop recommendations, and take votes as necessary.

DSMB Recommendations

DSMB recommendations should be based on results for the trial being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the principal investigator to ensure that the DSMB is kept apprised of non-confidential results from other related studies that become available. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

The PI will be responsible for submitting DSMB progress reports the CTSRMC, to the sponsor/funding agency and the IRB.

If the DSMB recommends that a study be changed for patient safety or efficacy reasons, or that a study be closed early because of slow accrual, the trial principal investigator must act to implement the change as expeditiously as possible. In the unlikely situation that the trial principal investigator does not concur with the DSMB, then the CTSRMC must be informed of the reason for disagreement. The trial principal investigator, DSMB chair, and the CTSRMC will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be maintained during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and/or CTSRMC members to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for other than patient safety or efficacy reasons or for slow accrual, the DSMB will provide an adequate rationale for its decision.

Release of Outcome Data

In general, outcome data should not be made available to individuals outside of the DSMB until accrual has been completed and all subjects have completed their treatment. At this time, the DSMB may approve the release of outcome data on a confidential basis to the trial principal investigator for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the DSMB's recommendation for general dissemination of results must be reviewed and approved by the DSMB.

Confidentiality procedures

No communications, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB except as provided for in this policy. Outcome results are strictly confidential and must not be divulged to any non-member of the DSMB. Each member of the DSMB, including non-voting members, must sign a statement of confidentiality.

Conflict of Interest

DSMB members are subject to the University of Pennsylvania policies regarding standards of conduct. Individuals invited to serve on the DSMB, as either voting or non-voting members will disclose any potential conflicts of interest, whether real or perceived, to the trial principal investigator and the CTSRMC, in accordance with the institution's policies. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest. Potential conflicts that develop during a members tenure on a DSMB must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest or the appearance of conflicts of interest may participate in a DSMB will be made in accordance with the institutions policies.

APPENDIX D
University of Pennsylvania Cancer Center
Policy and Procedures for Auditing Clinical Protocols

Data Safety and Monitoring Committee (DSMC)

The Data Safety and Monitoring Committee provides independent oversight of clinical trials conducted at the ACC. The DSMC is chaired by Dr. David Vaughn. The DSMC meets monthly to review all aspects of the conduct of ongoing clinical research protocols that have been approved by the CTSRMC. Administrative Director of the DSMC is Ms. Vicki Sallée. Vicki is also the Compliance Officer for the ACC. She is responsible for the overall organizational management of the DSMC and reports directly to the chair of the subcommittee. She is available to answer any questions or provide additional assistance and can be reached at 215-349-5238 or vsallee@mail.med.upenn.edu.

In addition to the functions described in the institutional Data Safety and Monitoring Plan, the DSMC conducts independent audits of CTSRMC approved trials. The DSMC provides quality control (QC) and quality assurance (QA) for the clinical protocols conducted at the UPCC.

Quality Control (QC)

The QC function ensures that the rights and well being of subjects are protected through education, training, guidance documents and meetings. The University of Pennsylvania also requires all PIs and his/her staff to obtain University of Pennsylvania certification in the conduct of clinical research. The certification program is in compliance with NIH requirements.

Quality Assurance

The QA function assures that the rights and well-being of subjects are protected through periodic audits. The audit will be an independent examination of trial related activities, documents and processes. The purpose of these audits is to assess compliance with regulations, and guidelines, as well as to determine integrity of data and to educate and train the study staff. The DSMC procedures will verify that the PI's conduct of the study reflects the data reported.

DSMC Audit Responsibilities

DSMC will audit all CTSRMC approved therapeutic clinical protocols. The frequency of the audits depends upon the risk of the protocol and the study sponsor.

Audits: Investigators will be notified five (5) weeks in advance of the scheduled audit. A random selection of three (3) subjects or 10% of the total accrual, whichever is higher (up to 25 subjects), will be audited.

Conducting the Audit: The auditor will review all of the following:

- Regulatory documentation and compliance
- Informed Consents
- Accrual rates
- Eligibility criteria
- Treatment administration and accountability
- Adverse/Serious Adverse Events and toxicities
- Response assessment
- Patient follow-up

- Data completeness
- Source documentation to Case Report Form (CRF)
- Overall organization and study related knowledge of staff

All discrepancies, omissions or queries will be recorded on the Audit Form.

Audit Deficiencies

Deficiencies will be recorded on the Audit Form and evaluated by the DSMC. The PI will be notified in writing of the audit findings and level of the deficiencies. Deficiencies will be identified as Minor, Moderate and Major.

Minor Deficiencies: Minor deficiencies are defined as those that do not impact on the data quality, safety and/or integrity of the study.

Corrective Actions: Upon notification of deficiencies, the PI and his/her staff are required to correct the deficiencies and develop a plan that will prevent such deficiencies in the future. The DSMC will not require a copy of the plan and the findings will not warrant an unscheduled re-audit of the study.

Moderate Deficiencies: Moderate deficiencies are defined by the DSMC as those that may have an impact on data quality or identify process problems. Deficiencies that affect data quality should appear in less than 50% of the sampled data.

Corrective Actions: Upon notification of deficiencies, the PI and his/her staff are required to correct the deficiencies and develop a plan that will prevent such deficiencies in the future. The DSMC will require a copy of the plan or a letter outlining corrective actions as a response to the audit notification. The findings will not warrant an unscheduled re-audit of the study.

Major Deficiencies: Major deficiencies are defined by the DSMC as those that heavily impact the data quality, safety and/or integrity of the study. The IRB and OHR will be notified of all internal audits that identify major deficiencies once a full assessment of the study has been made. Identification of major deficiencies may result in the investigator being placed on temporary suspension and patient enrollment will be halted.

Corrective Actions: Upon notification of deficiencies, the PI and his/her staff are required to correct the deficiencies and develop a plan that will prevent such deficiencies in the future. The DSMC will require a copy of the plan or a letter outlining corrective actions as a response to the audit report within 10 business days of receipt of the audit notification. The findings will warrant a re-audit of the study within 60 days of the scheduled audit. If the deficiencies are not corrected, the DSMC will re-evaluate the study and take whatever corrective actions it deems necessary to protect the participants, ACC and The University of Pennsylvania. If the results of the re-audit are acceptable, the DSMC may re-open the study.

Auditing Frequency

The frequency of the audits depends on the Monitoring Plan and risk level submitted by the P.I. and approved by CTSRMC. Issues to consider include the size, complexity, progress of enrollment and any special considerations described in the study protocol. The auditing frequency also depends upon the study sponsor (i.e. Cooperative group, Pharmaceutical/Industry, NCI (CTEP approved), or Investigator-initiated studies).

The extent of DSMC monitoring/auditing is dependent upon many factors including the trial sponsor and risk.

- **NCI Cooperative Groups**

The DSMC randomly selects cooperative group trials for auditing. The random selection will allow for a sampling across groups and disease sites. Additionally, the DSMC requires the PI to provide a copy of all inspection reports conducted by the respective group to the committee for review. All SAEs on subjects enrolled on these studies must be reported to the DSMC for review. Based on local or national/external SAEs reported, the DSMC has the authority to close any active study to further local accrual and/or require more detailed reporting of SAEs observed and a description of steps taken to minimize patient risk and maximize the safety of subjects.

- **NCI/CTEP Sponsored Other NCI Contracts**

These studies are audited by the DSMC based on the risk level assigned by the CTSRMC. All SAEs on subjects enrolled on the study must be reported to the DSMC. Based on local or national/external SAEs reported, the DSMC has the authority to close any active study to further local accrual and/or require more detailed reporting of SAEs observed and a description of steps taken to minimize patient risk and maximize the safety of subjects.

- **Pharmaceutical/Biotechnical Industry**

The DSMC randomly selects industry sponsored trials for auditing. The random selection will allow for a sampling across sponsors and disease sites. Additionally, the DSMC requires the PI to provide a copy of all inspection reports conducted by the sponsor to the committee. All SAEs on subjects enrolled on these studies must be reported to the DSMC for review. Based on local or national/external SAEs reported, the DSMC has the authority to close any active study to further local accrual and/or require more detailed reporting of SAEs observed and a description of steps taken to minimize patient risk and maximize the safety of subjects.

- **Investigator Initiated Studies**

These studies are audited by the DSMC as required by the risk level assigned by the CTSRMC. All SAEs on subjects enrolled on the study must be reported to the DSMC. Based on SAEs reported, the DSMC has the authority to close any active study to further accrual and/or require more detailed reporting of SAEs observed and a description of steps taken to minimize patient risk and maximize the safety of subjects. In addition to DSMC auditing, the CTSRMC may request that the DSMC provide a real-time study monitor for certain high risk in-house studies. In this case, the DSMC Administrative Director will meet with the study PI to establish a plan which will define the frequency and intensity of DSMC monitoring. The areas including in the plan will be inspection intervals, study aspects, regulatory documents and agent accountability (where applicable). The DSMC monitor will make on-going suggestions to the PI for study improvement which may require changes to established processes to ensure continued subject safety and collection of high quality data.

CTSRMC Role in External Audits

Audits conducted by NIH/NCI, cooperative groups and/or on behalf of these groups; or the FDA are considered external audits. The DSMC will work with the PI and his/her staff to help prepare for all external audits including an evaluation of all study documents, identifying deficiencies and helping correct them, arranging the location of the audit as well as the availability of all study staff, the pharmacist and any other relevant participants. Along with organizing the study data and participants, the DSMC will act as the liaison between the PI and the external monitoring agency.

Immediately upon notification of an external audit, the PI is responsible for contacting the DSMC and providing the following:

- Study Name
- UPCC Number
- IRB Number
- Agency conducting the audit
- Name(s) and telephone number(s) of the person(s) conducting the audit
- Date and time of the audit

The DSMC will notify the OHR and the IRB. However, the PI is responsible for notifying all other applicable office(s)/department(s) (e.g. Pharmacy, Lab, Medical Records).

Notifying OHR: The DSMC will notify the OHR of all FDA and NIH/NCI audits and the outcome of all such audits. If during the course of preparing for an audit, the DSMC finds areas of concern, the committee will evaluate the concerns, assess the impact and notify OHR accordingly. The DSMC will continue to coordinate and organize all aspects of the audit preparations and notify OHR of the outcome.

Preparing for an External Audit: To facilitate the audit of a study, which includes both the data and processes, the PI and his/her staff should ensure that all documents (CRFs, source documents, agent accountability records and regulatory files) for the study are available and organized.

CRFs: All study CRFs should be arranged in a folder or binder.

Source Documents: Source data must exist for all the data points collected on the study specific CRFs. Originals should be tagged to identify the corresponding CRF page.

Investigational Agent Accountability:

All investigational agents (drugs and devices) received, used and destroyed/returned during the course of a clinical trial must be carefully documented in accordance with all regulations. The following documents must be organized and available:

- Sample of label(s)
- Handling instructions
- Shipping and receiving
- Certificate of analysis (agents manufactured on campus and Sponsor-investigator studies)
- Un-blinding/masking (procedures)
- Master randomization list
- Final agent accountability log (received, dispensed, returned to site, returned to sponsor or destroyed)

Regulatory Documents: Regulatory documents are also known as “Essential Documents”. These represent the quality, integrity and conduct of the study. All regulatory documents should be arranged in a folder or binder that identifies:

- Protocol Name
- UPCC Number

- Sponsor
- PI(s)
- Site Code (where applicable)
- Participant ID
- Participant Initials

Since ACC study documentation may vary, the following documents, minimally, should be organized and available:

- Investigator's Brochure and updates (where applicable)
- Signed protocol and amendments
- Sample CRFs and amendments
- Informed consent forms and amendments
- Study related advertisements
- Approvals and re-approvals from IRB, CTSRMC and all other applicable departments (e.g. Radiation Safety) of the following:
 - Protocol and amendments
 - CRF
 - Informed Consent
- Approvals from appropriate Regulatory Authorities (FDA, NIH/NCI)
- Current CVs of all investigators and sub-investigators
- 1571 or 1572 if applicable
- Lab certifications and updates
- Lab normal values/ranges and updates
- Certification/accreditation or QC/ validation for medical/laboratory test (if applicable)
- Record of retained body fluids/tissue samples (if applicable)
- Enrollment log
- Investigational Agent accountability (if applicable)
- Monitoring and CTSRMC audit reports
- Correspondence with IRB, CTSRMC and Sponsor (e.g. document phone calls, letters, meeting minutes)
- SAE notifications and updates to IRB, DSMC and Sponsor
- Copy of Sponsor's notification to regulatory authorities of SAE/ADRs.
- Interim/annual reports to IRB and CTSRMC
- Final report (Investigator held INDs and Investigator-Initiated studies)
- Clinical study report (Investigator held INDs and Investigator-Initiated studies)

APPENDIX E

Requirements for Studies Involving On-Campus Manufacturing of Investigational Agents

Agents manufactured on-campus for use in clinical trials must be manufactured in accordance with appropriate GMP concepts. Each manufacturer should establish, document, and implement an effective system for managing quality in accordance with all DSMC and the University of Pennsylvania guidance documents as well as with all applicable guidelines and regulations. The following steps are required to carry out his/her obligations:

- Initial Assessment monitoring to serve as early detection and to help identify trouble areas in procedures and/or staff early enough to allow corrections which will benefit the manufacturer and/or study long term.
- Pro-actively addressing and resolving problems with staff and/or procedures.
- Documentation of all corrective actions.
- Open, timely and documented communication with the IRB and the CTSRMC.
- All quality related activities should be defined in the protocol and documented at the time they are performed.
- Any deviation from established procedures should be documented, explained and reported to the sponsor (where applicable), the IRB and the CTSRMC.
- Every change in production, specifications or test procedures should be recorded and reported to the sponsor (where applicable), the IRB and the CTSRMC.
- The following should be reviewed and monitored in a timely manner:
 - Release or rejection of all agents, raw materials and intermediates.
 - Completed manufacturing records for critical process steps before release of the agent.
 - Investigation and resolution of critical deviations.
 - Procedures and approval of changes potentially impacting the quality of intermediates or agents.
 - Validation protocols and reports.
 - Systems used for maintaining and calibrating critical equipment.
 - Testing of material and stability data to support retest, expiration dates and storage conditions on intermediates and/or agents where appropriate.
 - Cell Bank maintenance and records (where applicable)
 - Laboratory Controls
 - Product storage and handling
 - Product quality