

Abramson Cancer Center of the University of Pennsylvania

Institutional Data Safety and Monitoring Plan

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TABLE OF CONTENTS

SECTIONS	PAGE
INTRODUCTION	4
ACC RISK CATEGORIES FOR STUDIES	5
CLINICAL TRIALS SCIENTIFIC REVIEW AND MONITORING COMMITTEE (CTSRMC)	6
Overview of CTSRMC	6
Clinical Research Categories Reviewed	6
Trial/Study Types Reviewed	6-7
Submission of Protocols to the CTSRMC	7
Submission of Protocols to the PPRC	7
Submission of Protocols to the SRC	7
CTSRMC Review of Protocols	7
Types of Review	8
SRC Scientific Review of Protocols	8
Committee Review of Protocols	8-9
Protocol Approval Criteria	9-10
Investigator-Initiated Multi-Site Studies	10
ACC Defined Essential Monitoring Plan Elements	10
Monitoring Plan Requirements for Clinical Trials Involving Agents Manufactured on Campus	10
Procedure for Submission of a Monitoring Plan to the CTSRMC	10
Review of Laboratory-Based Studies	11
Process and Criteria for Prioritizing Protocols	11
Relationship of CTSRMC and IRB	11
Time To Activation	11
Monitored Protocols for Progress and Performance	11-12
IND Evaluation	12
DATA AND SAFETY MONITORING COMMITTEE (DSMC)	13
Overview of the DSMC	13
Overview of the CRQA	13
Relationship of DSMC and CRQA	13
Responsibilities of the DSMC	13-14
Monitoring Plans	14-15
Study Exceptions and Deviations	15-16
Auditing and Monitoring Timelines	16
Procedures for DSMC Review of Protocol Compliance	16
Audit Outcomes	16-17
PI Response to Audit Letter	18
Additional Monitoring Required by the DSMC	18
Pharmacovigilance (PV)	18-19
Serious Adverse Events (SAEs)	19
Reporting Events	19
DEPARTMENT OF COMPLIANCE AND MONITORING (DOCM)	20
Overview of the DOCM	20
Auditing by Sponsor Type	20
Monitoring	20-21
Distance Monitoring	21

Auditing and Monitoring Timelines	21-22
Audit Criteria and Procedures	22-23
Areas Reviewed During Monitoring/Auditing Multi-Site Protocols	23
Electronic Versions of Source Documents	23
Audit Deficiencies and Audit Letter	23
HIPAA	23
DOCM Role in External Audits	23-24
Additional Inspections	24
RESPONSIBILITIES OF THE PRINCIPLE INVESTIGATOR (PI)	25
ADDITIONAL OVERSIGHT	26
University of Pennsylvania Human Subjects Protection Training/Certification	26
University of Pennsylvania Institutional Review Board (IRB)	26
Office of Human Research	26
TECHNOLOGIES	27
ADMINISTRATIVE INFORMATION	28
APPENDICES	29-106
Scientific Review Guide	30-33
Primary and Secondary Reviewer Evaluation and Scoring Form	34-35
Statistical Reviewer Evaluation Form	36-37
Multi-site Justification Form	38-40
Template Monitoring Plans	41-44
On-campus Manufacturing of Investigational Agents/Products	45
IND Exemption Determination	46-50
Definitions, Terminology and Reporting Requirements	51-60
Multi-site Manual of Procedures Template	61-63
Exemption and Deviation Log Templates	64-65
Guidelines Regarding Data and Safety Monitoring Boards (DSMB)	66-68
GMP Inspection Checklist	69-78
GLP Inspection Checklist	79-89
GTP Inspection Checklist	90-105
21CFR11 Closed System Checklist	106-109

I. 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 and the quality. In response to the NIH/NCI policy requiring 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 investigator and institutional monitoring, auditing and oversight of studies at the ACC and its matrix (collectively referred to as the ACC).

ACC established a comprehensive Quality Control (QC), Quality Assurance (QA), Regulatory Affairs (RA) and Pharmacovigilance (PV) system for all cancer based human subject research. This system was first established in September 2001 and has continued to evolve to fit the requirement of NCI and the needs of the ACC. The ACC has approached human subject protection through three functional entities; the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC), the Data and Safety Monitoring Committee (DSMC) and the Department of Compliance and Monitoring (DOCM).

Institutional Data Safety and Monitoring Plan

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

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 subjects 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 DSMC 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 PI, subject to review and approval by both the DSMC and the CTSRMC.

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

1. Protocols differ substantially in complexity and risk and no pre-determined 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 must 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, 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.

TABLE 1: ACC Risk Categories for Studies

Low Risk	Moderate Risk	High Risk
<ul style="list-style-type: none"> • Study poses limited risk compared to that experienced in daily life (blood draw, physical exam, psychological testing, residual collecting, some imaging). • Non-interventional Behavioral, Outcome, Epidemiologic, Prevention, Diagnostic, Supportive, Screening or Observational studies • Nutrition studies (not including dietary supplements being used as a nutraceutical) • Survey/Questionnaire Studies • Biospecimen collection/banking • Retrospective chart reviews • De-identified genetics studies 	<ul style="list-style-type: none"> • Subjects treated with placebo for a recognized disease • Substantial risk (>5%) of a Serious Adverse Event (SAE) originating from the underlying condition of the enrolled subject • Sponsored Phase I or II study with sufficient safety data in humans • Sponsored Phase III study • Post marketing study Phase IV or post marketing intervention/device study (as defined by FDA). • Some industry and cooperative group sponsored interventional studies (as determined by CTSRMC) • Sponsored nutraceutical studies • Investigator-initiated studies requiring physical activity, exercise, acupuncture or acupressure • Identified genetics studies 	<ul style="list-style-type: none"> • Involves an invasive procedure with significant risk (as determined by CTSRMC) • Any investigator-initiated intervention trial (with or without IND/IDE) • Implantation of device/agent with or without an IND or IDE • Involves the use of a new chemical or drug for which there is little/limited 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 multi-center study* • An investigator-initiated randomized Phase III clinical study# • Study has provisions to waive consent in emergency circumstance • Involves enrollment of vulnerable population(s)

*May require a Medical Monitor or Safety Monitoring Committee as determined by CTSRMC

Requires a Data Safety Monitoring Board.

The amount of oversight provided by a study sponsor, who may be NIH, NCI, CTEP or a pharmaceutical or biotechnology company impacts the amount of monitoring or auditing required for a study.

CLINICAL TRIALS SCIENTIFIC REVIEW AND MONITORING COMMITTEE (CTSRMC)

Overview of CTSRMC

When the CTSRMC was officially established by the ACC in 1992, the Dean of the School of Medicine affirmed the Committee as the required body within the School of Medicine for reviewing and approving all cancer-related protocols prior to University IRB approval. In 2003, following a number of leadership changes in the Human Subjects Research infrastructure at the University of Pennsylvania, the School of Medicine reaffirmed its commitment to supporting the mission of the ACC PRMS, and has worked collaboratively with the ACC to achieve the mission outlined by NCI in the CCSG. No cancer-related protocol may initiate subject enrollment at Penn without first receiving both IRB and CTSRMC approval. Because the ACC recognizes the role human subjects research plays in providing treatment options to subjects and expanding our knowledge of this life-threatening disease, the CTSRMC Chair and Administrative Director work closely with and report directly to the Cancer Center Director. The CTSRMC is fully integrated into the clinical trials review and approval systems of the School of Medicine and University. The Committee functions in a coordinated manner with the IRB, Office of Research Services, and various other review entities including Environmental Health and Radiation Safety, Biosafety, and Investigational Drug Services. Consistent with NCI Core Grant guidelines, the CTSRMC reviews the scientific merit, scientific priorities, and scientific progress of all cancer-related protocols with the exception of protocols sponsored by NCI designated cooperative groups. Although these protocols are excluded from initial CTSRMC scientific peer review, they are evaluated for prioritization before opening and ongoing scientific progress. The following are recognized by the CTSRMC as qualified Cooperative Groups: American College of Surgeons Oncology Group (ACOSOG), American College of Radiology Imaging Network (ACRIN), Bone Marrow Transplant Clinical Trials Network (BMT-CTN), Cancer and Leukemia Group B (CALGB), Children's Cancer Group (CCG), Children's Oncology Group (COG), Eastern Cooperative Oncology Group (ECOG), Gynecological Oncology Group (GOG), New Approaches to Brain Tumor Treatment (NABTT)/Adult Brain Tumor Consortium (ABTC), New Approaches to Neuroblastoma Therapy (NANT), National Surgical Adjuvant Breast Project (NSABP), National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), Pediatric Brain Tumor Consortium (PBTC), Radiation Therapy Oncology Group (RTOG) and Southwest Oncology Group (SWOG).

Clinical Research Categories Reviewed

- Involving an agent or device *with* therapeutic intent
- Involving *other types* of interventions (i.e. behavioral modification, nutrition, exercise, counseling, etc.)
- Involving *no* intervention

Trial/Study Types Reviewed

- **Therapeutic:** therapeutic intent using drugs, radiation, surgery, other biological agents, or behavioral or other interventions.
- **Prevention:** for the modulation of cancer risk and inhibition of cancer progression using chemoprevention drugs, nutritional, dietary, behavioral, or other interventions.
- **Supportive Care:** intended to improve the comfort and quality of life for the patient using drugs, nutritional, dietary, behavioral or other interventions.
- **Screening, Early Detection or Diagnostic:** directly testing the efficacy of devices, techniques, procedures; or tests for earlier or more accurate detection or diagnosis of disease.
- **Epidemiologic, Observational or Outcome:** among cancer patients and healthy populations that involve no intervention or alteration in the status of the participants, e.g., surveillance, risk assessment, outcome, environmental, and behavioral studies.
- **Ancillary:** studies that are stimulated by, but are not a required part of, a main clinical trial/study, and that utilize patient or other resources of the main trial/study to generate information relevant to it.

- **Correlative:** Laboratory based studies using specimens to assess cancer risk, clinical outcomes, response to therapies, etc.

Submission of Protocols to the CTSRMC

All cancer-related protocols that are not sponsored by an NCI designated cooperative group are reviewed by the CTSRMC. Although not required to review peer-reviewed protocols, the CTSRMC has continued to do so as part of the Committee's ongoing commitment to ensuring the feasibility and quality of research ACC-wide. There are several steps researchers are encouraged to take prior to submitting a protocol. These include: scheduling a meeting with a member of the Biostatistics Core to ensure that the protocol has a sound statistical plan; consultation with the Clinical Research Unit to review the protocol's project and data management needs; discussion with the DSMC to ensure that the protocol meets all applicable regulatory requirements and has a sound monitoring plan; and review of the protocol with CTSRMC staff to ensure the protocol is complete. Investigators must electronically submit a complete protocol packet containing the review face sheet, current protocol, current study and HIPAA consents, Study Monitoring Plan, CRF's (in-house), Investigator's Brochure (where applicable) and documentation of IND/IDE exemptions/acknowledgement where applicable. Complete packets must be received no later than the 20th day of the month in order to have it reviewed at the CTSRMC meeting the following month. CTSRMC meetings are held on the second Monday of every month. Grant applications are not considered protocols and are not accepted by the Committee for review.

Submission of Protocols to the PPRC

All pediatric cancer-related protocols that are not sponsored by cooperative groups are reviewed by the PPRC. However, they are evaluated for feasibility and prioritization. As with the CTSRMC, pediatric researchers are encouraged to meet with key content experts for evaluation of the quality and completeness of their protocols prior to submission to the PPRC. Investigators must submit a complete protocol packet (protocol, consent, CRFs, and other applicable documents) two weeks prior to the following month's meeting.

Submission of Protocols to the SRC

Because POHA primarily conducts peer-reviewed research, their central administrative office is responsible for downloading protocols from all applicable sources and distributing them to relevant Committee members two weeks prior to the following month's meeting. POHA is involved with a few industry protocols. These protocols must be distributed to Committee members one month prior to the following month's meeting to allow for sufficient time to conduct a scientific review.

CTSRMC Review of Protocols

The CTSRMC reviews protocols by either an expedited or full-Committee mechanism. Expedited review protocols are always reviewed by at least the Chair, Administrative Director, and Biostatistician. However, at the discretion of the Chair, additional review for specific expertise may be sought from Committee members. Full-committee protocols are assigned to a primary, secondary, and biostatistical reviewer. The primary reviewer will have expertise in the protocol's targeted disease. In addition to assigned reviewers, all protocols are reviewed for regulatory issues by the Administrative Director. The CTSRMC has developed a Scientific Review guidance document to train new reviewers and to steer the ongoing review process. The document covers concepts such as how to evaluate the rationale, scientific design and objectives, feasibility and competitiveness of the study; how to evaluate the completeness of the protocol, and evaluating the design based on the stated Phase (*Appendix A*). A third category of protocols evaluated by the CTSRMC are "exempt from review" which are evaluated by the Administrative Director to ensure they meet the criteria for exemption and for competitiveness. Investigators receive an exemption acknowledgement letter for their records.

Types of Review

Exempt

- Retrospective chart reviews, no consent, de-identified data
- Residual specimen collection, no consent, specimens are de-identified

Expedited

- Most “other intervention” and “no intervention” protocols

Full

- All therapeutic intervention; some “other intervention” protocols

PPRC Scientific Review of Protocols

The PPRC reviews protocols by either an expedited or full-Committee mechanism. Expedited review protocols are always reviewed by at least the Chair and Biostatistician. However, at the discretion of the Chair, additional review for specific expertise may be sought from Committee members. Full-Committee protocols are assigned to a primary, secondary, and biostatistical reviewer. The primary and secondary reviewers will have expertise in the protocol’s targeted disease and/or modality. Review is not limited to those assigned to the protocol. Feedback from all members is sought and encouraged. The PPRC uses the Scientific Review guidance developed by the CTSRMC to train new reviewers and to steer the ongoing review process.

Types of Review

Expedited

- Most “other intervention” and “no intervention” protocols

Full

- All therapeutic intervention; some “other intervention” protocols

SRC Scientific Review of Protocols

The SRC only conducts full review of applicable protocols. Because the majority of POHA SRC protocols are cooperative group, CTEP, or other peer-review studies, these protocols are evaluated for applicability to their center, patient population, and current standard of practice, in addition to competition with other currently open protocols. A very small percentage of SRC protocols are industrial. These protocols receive full scientific review in accordance with the standards set by the CTSRMC. Full-Committee protocols are assigned to a primary and secondary reviewer. Both reviewers will have expertise in the protocol’s targeted disease and/or modality. Review is not limited to those assigned to the protocol. Feedback from all members is sought and encouraged. The SRC uses the Scientific Review guidance developed by the CTSRMC to train new reviewers and to steer the ongoing review process.

Types of Review

Full

- All protocols

Committee Review of Protocols

When a protocol is scheduled for review, the PI is sent a notice of review and is expected (although not required) to attend the review of his/her protocol. No less than ten days prior to every meeting, Committee members are notified that the electronic study packets are available through the CTSRMC’s secure website. In addition, assigned reviewers download a protocol review form to document their review and stipulations. All Committee members are actively encouraged by the Chair to comment and critique studies under consideration. Should a Committee member be unable to attend a meeting, comments can be submitted via e-mail to the CTSRMC Office to be read by the Chair during the meeting.

During the Committee meeting, the primary, secondary, biostatistical, and regulatory reviewers discuss the study in detail, including the study design, appropriateness for the institution and patient populations, feasibility of conducting the protocol, statistics, sufficiency of the monitoring plan, competing protocols, operational issues, and institutional needs. Comments made by the scientific and biostatistics reviewers, along with other issues identified during the full Committee review, are included in the Committee's minutes, and are subsequently included in the letters sent by the Committee to PIs. Most members also provide comments based on their area of expertise during meetings whether or not assigned a protocol for review. The open exchange of information, thoughts, and critiques adds important depth to the level of review. Depending on the Committee's vote, the protocol may be fully approved, approved with stipulations, or disapproved. SRC accepts or declines protocols. Studies that have not been disapproved are assigned a risk level, which dictates the required level and frequency of DSMC auditing or prospective monitoring. Protocols that were disapproved require a full re-review by the Committee to gain approval.

Satisfactory resolution of all deficiencies identified by the Committee must be received before a protocol will be granted full approval. After receiving the revised protocol and formal response to the Committee's critique, the CTSRMC Chair and other applicable reviewers re-evaluate the protocol. Protocols approved with stipulations are reviewed in their revised form by the Chair and, as appropriate, may be approved by the Chair with no further action required by the Committee. Protocols with statistical revisions are re-reviewed by the original statistical reviewer. Protocols with regulatory or quality assurance stipulations must be approved by the CTSRMC Administrative Director. No protocol may be approved without the full approval of representatives from the key technical areas. Final CTSRMC approval letters are forwarded to the University's IRB.

Protocol Approval Criteria

Protocols must minimally fulfill the following requirements for approval (*Appendices B and C*)

- scientific rationale with definitions of research objectives and approaches
- accrual goals with justification of accrual rates
- clear outline of inclusion/exclusion criteria
- compliance with informed consent procedures
- detailed treatment plan and schedule
- provisions for dose modification and toxicity management
- description of the investigational agent to be studied
- reporting mechanism for adverse reactions
- criteria for evaluation and endpoint definitions
- statistical analysis plan including sample size, stratification (when appropriate), method of statistical analysis of collected data and anticipated duration of the trial given sample size predictions
- in-house protocols must have a local statistician assigned
- a monitoring plan commensurate with the type of protocol

Review is not limited to those assigned to the protocol. Feedback from all members is sought and encouraged. The CTSRMC has developed a Scientific Review guidance document to train new reviewers and to steer the ongoing review process. The document covers concepts such as how to evaluate the rationale, scientific design and objectives, feasibility and competitiveness of the study; how to evaluate the completeness of the protocol, and evaluating the design based on the stated Phase.

Investigator-initiated studies must have case report forms to show a well thought out plan for collection of study data. The CTSRMC, along with the the IRB, has developed a protocol template to guide investigators in the development of protocols. Investigators are also advised to compare protocols provided by outside entities against the template to ensure completeness prior to

submission to the CTSRMC. Pediatric protocols use the COG model for development of institutional studies.

Investigator-Initiated Multi-Site Studies

In accordance with University of Pennsylvania policies, the CTSRMC has established a justification process for investigators interested in opening investigator-initiated studies at entities not considered Abramson Cancer Center with the goal of ensuring high quality research. Investigators must submit the justification form (*Appendix D*) with the study protocol. The CTSRMC reviews the justification request and determines whether or not this type of study should be opened outside the Cancer Center, if the selected sites are appropriate and whether the PI can conduct this type of study. Additionally, the CTSRMC may, at its discretion, set restrictions on the number of sites open outside the Cancer Center for a particular study, a particular investigator or a particular group. The CTSRMC may also, at its discretion, set restriction on the number of multi-site studies any one investigator may have open at the same time. The study may not open at any non Cancer Center site without CTSRMC approval of the justification.

ACC Defined Essential Monitoring Plan Elements

In general, a MP (*Appendix E*) should list who will be responsible for monitoring, the frequency of review, what aspects of the study will be inspected and identification of reporting requirement for adverse events, detail other forms of external monitoring/auditing and identify other review entities such as a Medical Monitor or Data and Safety Monitoring Board.

Monitoring Plan Requirements for Clinical Trials Involving Agents Manufactured on Campus

Clinical trials that are conducted in the Cancer Center 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) and GLP (Good Laboratory Practice). Examples of these types of clinical trials include vaccines; adoptive therapies, gene transfers, etc. Trials such as these may require a Medical Monitor, Safety Monitoring Committee or Data and Safety Monitoring Board (at the discretion of the CTSRMC) as well as personnel with expertise in GLP and GMP. The PI must develop a custom comprehensive monitoring plan under the guidance of the CTSRMC. This plan must receive approval from the DSMC before the study can receive full CTSRMC approval (*Appendix F*).

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 properly and that all the required components of the study protocol are present which is required before the submission is accepted by 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 the 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 E* of this document. These can be downloaded from our website www.ctsrc.org.

Review of Laboratory-Based Studies

Correlative or laboratory-based studies are reviewed via an expedited mechanism at the discretion of the Committee Chair. The Chair may decide after reviewing a protocol that it warrants full Committee review.

Process and Criteria for Prioritizing Protocols

The process for prioritizing clinical protocols lies initially with disease-specific teams. Investigators in all cancer relevant departments are aware of the CTSRMC's expectations for prioritization, as these expectations are posted on the Committee's website, are documented in the ACC Institutional Data and Safety Monitoring Plan, and are sent as a reminder message every time a protocol is submitted for a UPCC#. The CTSRMC expects that all protocols that are submitted have been reviewed by the disease programs for appropriateness prior to being added to their research portfolios. Additionally, the CTSRMC administrative office generates a monthly report on all potentially competing protocols currently open campus wide. The Chair discusses each protocol on the list of potential competitors as part of the review process with the entire Committee, and asks the PI of the protocol under review to comment on the potential competing protocols. If an overlapping protocol is identified, the PI is asked to provide a formal prioritization management plan as part of his/her stipulation response. Protocols will not receive full approval until the Chair is satisfied with the proposed plan. In addition, all protocols using the Clinical Research Unit must first be reviewed by the Strategic Planning and Resource Committee (SPARC), which is an operations feasibility review committee. For studies using these core resources, the CTSRMC will not accept a protocol for review without first having documentation of SPARC approval. SPARC approval ensures that protocols using core resources have sufficient staffing and funding resources. Also, although NCI designated cooperative group protocols are not reviewed for scientific merit, they are administratively reviewed for prioritization and competitiveness.

Relationship of CTSRMC and IRB

Both the University of Pennsylvania's IRB, which operates through the Office of Research Administration, and the CHOP IRB, are completely separate from the CTSRMC mechanisms at these institutions. The roles of the CTSRMC and its Sub-Committee and the institutional IRB's are complementary, not overlapping. The primary focus of the CTSRMC is to ensure that protocols have scientific rationale, merit, feasibility, and appropriate statistical designs, as well as appropriate plans for prioritization. The major focus of the institutional IRB review is subject safety, ethical concerns, and informed consent procedures. The University of Pennsylvania's IRB and CHOP's IRB will not grant final approval for a cancer-related protocol to be open to enrollment until final approval is granted from the CTSRMC. This agreement has been in place at the University of Pennsylvania since 1992 and Children's Hospital since 2001. POHA protocols are reviewed by the University of Pennsylvania IRB.

Time To Activation

The time from CTSRMC, PPRC and SRC approval to the time of study activation (ready to enroll subjects) depends on a number of factors such as the rate at which the PI responds to stipulations, completeness of responses to stipulations, gaining final approval from the IRB and other required review bodies (i.e. Radiation Safety, Biosafety, NIH funded CTCRC [formerly TCRC] etc.) as well as resolving other administrative and operational items. The ACC Committees generally send initial review letters within one week of the monthly meeting and responds to addressed stipulations within two weeks of receiving the investigator's response.

Monitored Protocols for Progress and Performance

In addition to the initial review of protocols for approval, the CTSRMC conducts ongoing review of protocol progress and performance through close accrual monitoring and review of the Continuing Review documentation. Every protocol, regardless of sponsor or funding source, is evaluated for accrual performance three months from the date approved by the CTSRMC and every three months

thereafter. Since cooperative group studies do not receive formal CTSRMC approval, they are monitored for performance three months from the IRB approval date. Studies with aggressive accrual timelines are monitored for accrual commensurate with the protocol defined timeline. Based on the stated accrual goal and protocol duration, an assessment of accrual performance is made. Studies with low or no accrual at the initial three month evaluation are sent a letter requesting an explanation for the current state of accrual and a plan to improve enrollment. For CHOP and POHA protocols, the CTSRMC will consult with the PPRC and SRC Chairs in addition to sending an accrual letter. The CTSRMC Chair considers the PI's response, and decides whether to accept the response, allowing the study to remain open, or closing/terminating the study. The Chair may grant a three, six, nine, or twelve month extension at his discretion or as requested by a Sub-Committee Chair. At the next review cycle, if the protocol is still underperforming, the PI is asked to provide within ten business days, an explanation for poor enrollment, a plan for improving enrollment, and a justification for continuing the protocol. Sub-Committee Chairs are included in this correspondence. If the study is allowed to remain open, but has not improved enrollment by the next review window anniversary, the CTSRMC Chair will notify the PI and the Sub-Committee Chair, if applicable, that the Committee has closed the study. When a study is closed by the CTSRMC, the University's IRB or CHOP's IRB is notified of the change in study status.

IND Evaluation

The Abramson Cancer Center of the University of Pennsylvania and the Office of Human Research (OHR) has implemented a system to assist clinical investigators in determining the need for submitting an Investigational New Drug Application or Investigational Device Exemption to the FDA. This system is to provide regulatory guidance in reviewing information provided by an investigator against the current regulations. All requests for IND/IDE exemption involving agents/devices that will be used in cancer trials/studies should be sent to the CTSRMC via e-mail using the standard exemption form (*Appendix G*). Once the CTSRMC has reached a conclusion, a letter with an explanation as to why an exemption is warranted (or not) will be sent to the PI. A copy of the letter will be forwarded to the Office of Human Research for their files. A representative from OHR will contact the CTSRMC if there are questions/concerns about the IND exemption determination. OHR research will send an acknowledgment of the CTSRMC's determination to the IRB. The PI may appeal to the CTSRMC with additional information to further support the claim for exemption if s/he feels it is justified. In the event that the CTSRMC does not agree, the PI must submit an IND application to the FDA before the CTSRMC will grant the study final approval. The IND exemption form can be downloaded from our website www.ctsrc.org.

DATA AND SAFETY MONITORING COMMITTEE (DSMC)

Overview of the DSMC

The DSMC was created as the entity within the ACC responsible for ensuring that all cancer-related human subject studies are conducted in accordance with all federal (e.g. GCP, GMP, GLP, GEP, GTP, HIPAA, Part 11, FISMA etc.) and institutional policies with the goal of improving subject safety and data quality and integrity. The DSMC has oversight over all CTSRMC approved protocols conducted within the ACC and its extended community based practice, Pennsylvania Hematology Oncology Practices (POHA), as well as CHOP Oncology. The DSMC meets the second Monday of every month. This is a closed meeting. Therefore, PIs, Sub -Investigators and Study Coordinators are not invited to attend. Due to the sensitive nature of the review conducted during the meeting, guests are not allowed to attend these meetings.

Overview of the CRQA

CRQA was created in 2008 as the entity within CHOP responsible for ensuring that all pediatric cancer-related human subject studies are conducted in accordance with the same federal policies as adult studies and CHOP institutional policies. Prior to 2008, this responsibility was covered by the adult DSMC with representation from CHOP. Because the ACC understands the significant differences between adult and pediatric research, the DSMC felt these studies would be better evaluated by a robust pediatric-based committee that reports to the DSMC. CRQA meets the second Friday of every month.

Relationship of DSMC and CRQA

The DSMC is the overall parent committee that sets policies, standards and expectations for all aspects of QC, QA and RA for adult and pediatric studies. The DSMC Chair and Director established the structure, membership and interactions between both committees. The DSMC Director attends the CRQA meetings on a quarterly basis to ensure the committee functions in accordance with established policies and procedures. In addition, minutes are provided to the DSMC office within 10 business days of the conclusion of each meeting. The DSMC directs monitoring and auditing activities in CHOP Oncology and oversees all regulatory activities. Ongoing references to DSMC activities should be understood to include CRQA activities as well.

Responsibilities of the DSMC

The DSMC accomplishes its wide-spread QC, QA and RA initiatives through establishing standards for prospective study monitoring (QC), routine study auditing (QA), reviewing subject safety issues, evaluation of protocol deviations, review of on-site Adverse Events (AE) and both on and off-site Serious Adverse Events (SAE), assessment of SMPs and examination of evaluations conducted by industry site monitors, Medical Monitors and Data and Safety Monitoring Boards (DSMB). Documentation of compliance activities, pending QC/QA assessments, mandated corrective actions and a comprehensive table of event reports generated from the Pharmacovigilance (PV) database are reviewed at each meeting. Additionally, all deviations and external evaluation documentation since the last meeting are reviewed. The committee may request new or ongoing corrective actions and detail required aspects of the Corrective Action Plan (CAP) to improve study safety and quality. In the event the issue could potentially affect subject safety, the IRB is notified of Committee actions. The committee may also request follow-up information on AEs/SAEs and make recommendations in regards to the status of the study or consent form modifications if there are concerns about safety or quality. The oversight activities of the DSMC are in addition to the study-specific monitoring that the DSMC requires from the study PI. The DSMC, in consultation with the Cancer Center Director, has the authority to suspend or terminate a protocol, investigator or program for safety concerns and/or major audit deficiencies. In the event a suspension or termination is handed down, the IRB is immediately notified of the action and will concur, thus all activities will cease until issues are resolved to the DSMC's satisfaction.

The DSMC has the authority to suspend or terminate a trial for any subject safety concerns and/or major audit deficiencies.

Monitoring Plans

• Investigator-Initiated Studies

Investigator-initiated studies, including many studies with NIH, NCI, or CTEP support (e.g. funding, agents, supplies etc), 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 **in-house monitoring plan template** developed by the DSMC 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, Adverse Drug Reactions (ADR) and Serious Adverse Events (SAE) (*Appendix H*). This plan must receive approval from the DSMC before the study can receive full CTSRMC approval.

• Multi-Institution Investigator-Initiated Studies

While the ACC recognized the need to make certain studies available to other non Cancer Center investigators, the ACC is highly aware of all of the risks and responsibilities that come along with this process. Investigator-initiated studies, including many studies with NIH, NCI, or CTEP support (e.g. funding, agents, supplies etc) or studies with grant-in-aid funding or agent/device support from industry manufacturers that are open to sites not considered Cancer Center require extensive oversight by the PI, the DSMC and the Department of Compliance and Monitoring. In addition to completing the **in-house monitoring plan template**, the PI must develop a comprehensive study specific Manual of Procedures (*Appendix I*) that minimally includes:

1. Locations at which s/he plans to open the protocol
2. Description of how each site will be initiated with timelines.
3. Description how eligibility will be confirmed.
4. Description of how regulatory tracking.
5. Description of how data management.
6. Description of the exception/deviation process.
7. Description of Adverse Events (AE), Adverse Drug Reaction (ADR), Serious Adverse Event (SAE) and Serious Adverse Drug Reactions (SADR) will be managed and reported.
8. Description of coordinating (primary) site will oversight
9. Description of the Corrective Action Plan development as necessary.
10. Describe how treatment administration monitoring
11. Describe agent/device accountability
11. Describe the process for monitoring study progress
12. Describe Electronic Data Capture using Velos eResearch (EDC)
13. Describe early termination process
14. Describe how the site will be "closed out".

This manual must receive approval from the DSMC before the study can open at any of the planned external sites.

• NCI Cooperative Group Studies

The Cancer Center conducts clinical trials of American College of Surgeons Oncology Group (ACOSOG), American College of Radiology Imaging Network (ACRIN), Bone Marrow Transplant Clinical Trials Network (BMT-CTN), Cancer and Leukemia Group B (CALGB), Children's Cancer Group (CCG), Children's Oncology Group (COG), Eastern Cooperative Oncology Group (ECOG), Gynecological Oncology Group (GOG), New Approaches to Brain Tumor Treatment (NABTT)/Adult Brain Tumor Consortium (ABTC), New Approaches to Neuroblastoma Therapy (NANT), National Surgical Adjuvant Breast Project (NSABP), National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), Pediatric Brain Tumor Consortium (PBTC), Radiation Therapy Oncology Group (RTOG) and Southwest Oncology Group (SWOG). Each national group conducts a range a therapeutic and non-therapeutic studies. Because each group has FDA approved monitoring plans

in place to ensure subject safety and data quality, the CTSRMC requires the PI to submit a sponsored 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.

- **Industry Studies**

All clinical trials conceived and initiated by pharmaceutical or biotechnology sponsors with subsequent Cancer Center participation required the PI to complete a sponsored monitoring plan template that will provide for trial oversight that compliments that of the study sponsor. The protocol specific plan will adhere to industry and FDA specified guidelines. The Cancer Center's DSMC has developed a template that fulfills this requirement.

- **Other Externally Sponsored Studies**

Some Cancer Center studies may be sponsored by other academic centers, foundations, consortiums, groups or institutions that are not included in any of the above categories. Each protocol must have specific plans for local monitoring of the study. The PI must develop a comprehensive monitoring plan using the in-house monitoring plan template that provides for complete quality assurance of the study.

Study Exceptions and Deviations

In order to harmonize with the IRB, the DSMC has changed its designations from Deviations and Violations to Exceptions and Deviations.

Exception

A one time, intentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented IRB and DSMC approval is required.

- For exceptions on Industry or Cooperative group sponsored protocols, written approval must be obtained from the Sponsor prior to submitting your exception request to the DSMC.
- For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the DSMC.

Upon receipt of a deviation request, the DSMC (or only the Chair as appropriate) will review the request within 24 hours and notify the PI of the Committee's decision. The DSMC may request additional information to assist with the determination. The IRB will be copied on all exception decisions made by the DSMC.

Deviation

A one time, unintentional action or process that departs from the IRB and CTSRMC approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the CTSRMC within five business days and the IRB within ten business days.

Examples of Exceptions/Deviations that must be submitted (not meant to be inclusive)

May/can/have affects/affected subject safety. So, a subject missing a visit is not an issue unless a critical/important treatment or procedure was missed and must have been done at that specific time.

- Violate eligibility
- Dose adjustment
- Stopping criteria
- Affect sample size (adding more subjects, decreasing number of subjects, changing the number of subject in a specific arm/cohort)

Other deviations should be explained in a memo to file or on a deviation log (*Appendix J*).

Upon receipt of a deviation request, the DSMC (or only the Chair as appropriate) will review the report and notify the PI of the Committee's assessment of the impact of the deviation. The DSMC may request additional information to assist with the assessment. The IRB will be copied on all exception decisions made by the DSMC if the Committee believes the deviation affects subject safety or study integrity. The DSMC may also request the DOCM conduct follow-up compliance activities to address issues revealed by the deviation report.

Auditing and Monitoring Timelines

The extent of monitoring/auditing established by the DSMC is dependent upon many factors including the trial sponsor and risk. See Department of Compliance and Monitoring (DOCM) Auditing and Monitoring Timelines below for further details. Upon final CTSRMC approval, investigators will receive a letter from the DSMC specifying the monitoring and/or auditing frequency for the study.

Procedures for DSMC Review of Protocol Compliance

A major function of the Committee is reviewing the outcome of QC/QA activities and providing guidance on necessary actions. The purpose of these reviews is to ensure that documentation of research practices is of the highest quality, verify protocol adherence, ensure that all Federal and local regulations concerning human subject research are being fulfilled, and to help identify and correct system problems that may impact the conduct and/or quality of research. The system established by the DSMC for review is based on one of the most widely used models for management known as the Shewhart Cycle (based on the scientific method) which incorporates the concepts of Plan-Do-Check-Act (PDCA).

Plan —Establishing the objective and processes. This is accomplished through the development of our Institutional Data and Safety Monitoring Plan (DSMP) as required by NCI and the Study Monitoring Plan (SMP) required by the DSMC.

Do —Implementation of the process. This is achieved through selection of studies and subjects for review in the case of GCP, GEP, Part 11 and FISMA and facilities for GMP and GLP evaluations.

Check —Measuring progress and checking against expectations. QC is the “check” process and is carried out through monitoring visits. The monitor reviews study progress against the plan which is the approved study protocol.

Act —Analyzing the information provided during the check process and determining where to apply changes that result in improvement. QA is the “act” process and is carried out through evaluation of monitoring reports. Appropriate actions are taken to correct deficiencies and this is incorporated into either the Institutional DSMP or SMP.

The PDCA cycle may be modified as necessary. By routinely reviewing protocols, the DSMC can detect deficiencies and provide solutions and support for correcting identified problems.

Audit Outcomes

Deficiencies identified by the DOCM monitor/auditor will be evaluated by the Chair and Director. The PI will be notified in writing of the audit findings and required corrective actions. Deficiencies will be identified as Minor, Moderate and Major. The PI is asked to review the findings with his/her study team and notify the DOCM within five business days if there are mistakes in the audit report. All responses to audit or monitoring letters must be signed by the PI. Responses from only the coordinator/data manager will not be accepted. A final evaluation of the level of the study deficiencies will be made after the response window has passed.

Minor Deficiencies

Minor deficiencies are defined as those that do not impact on the data quality, subject 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 but will require a response to the audit letter. 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 25% of the sampled data. Greater than 25% may modify the deficiencies to the major category based on the overall impact on 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 may require a copy of the plan or request details of the plan be included in their response to the audit letter. The findings may not warrant an unscheduled re-audit of the study. The PI is given ten business days to respond to these finding. An evaluation of the deficiencies will be re-evaluated upon receiving the PI's response. At this time, if the DSMC Chair and the DDCM Director do not find the response satisfactory, the IRB will be alerted of the actions taken by the ACC. The DDCM Director will update the IRB of the corrective actions being taken and progress being made.

Major Deficiencies

Major deficiencies are defined by the DSMC as those that heavily impact the data quality, safety and/or integrity of the study. If a study is determined to have major deficiencies once the PI responds to the audit letter, the IRB and OHR (for SoM only) will be notified. Identification of major deficiencies may result in the investigator and/or the investigator's studies being placed on temporary suspension and subject 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 PI is given five business days to respond to these findings including development and implementation of the DSMC defined Corrective Action Plan (CAP). An evaluation of the deficiencies will be re-evaluated upon receiving the PI's response and CAP. At this time, if the DSMC Chair and DDCM Director do not find the response satisfactory, the IRB and OHR (for studies conducted by SoM faculty) will be alerted of the actions taken by the ACC. The DDCM Director will update the IRB and OHR (for studies conducted by SoM faculty) of the corrective actions being taken and progress being made. The findings will warrant a re-audit of the study within sixty days of the scheduled audit or at the discretion of the DSMC. For studies that do not have additional subjects to audit, the DSMC may, at its discretion, change the audit frequency upon additional enrollment (if applicable). If the deficiencies are not corrected, the DSMC will re-evaluate the study and take whatever corrective actions it deems necessary to protect subjects, Abramson Cancer Center and The University of Pennsylvania. Once the DSMC determines that the study and/or study team have achieved an acceptable level of quality, the DSMC will notify the IRB and OHR (for studies conducted by SoM faculty) that the deficiencies have been corrected, training has been completed, processes have been restructured and the PI and his/her team are allowed to conduct re-open their protocol(s) within the Cancer Center. If the results of the re-audit indicate there are still major deficiencies, the DSMC will evaluate ongoing compliance activities and communicate with the IRB and OHR (for studies conducted by SoM faculty) if it is determined that the deficiencies should be reported to the NCI/NIH, FDA or other regulatory body.

PI Response to Audit Letter

The findings on the audit form will be incorporated into a letter which will be sent to the PI. A copy of the audit letter will be forwarded to the Cancer Center Director and the applicable department chair and/or division chief if warranted.

In certain circumstances, a PI may request an extension of the response time identified in the audit letter. All requests must be received before the window has expired. Such requests must be in writing, explain the need for the extension and provide a date the response will be received. Responses must address all items identified in the letter and include supporting documentation as requested. Failure to respond to audit letters may result in suspension of the study until an acceptable response is received and reviewed by the DSMC

Additional Monitoring Required by the DSMC

- **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. At the CTSRMC's discretion, a Medical Monitor may be necessary for certain moderate risk studies as well.

- **Safety Monitoring Committee (SMC)**

A SMC is composed of two to three 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 subject 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 Committee reserves the right to recommend a DSMB where it believes necessary. 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. DSMB members must be primarily comprised of external members but certain expertise may be obtained internally if most appropriate. If possible, the PI 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 PI. 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 DSMC and CTSRMC prior to approval (*Appendix K*).

Pharmacovigilance (PV)

The DSMC plays a vital role in evaluating Adverse Events (AE), Adverse Drug Reactions (ADR), Serious Adverse Events (SAE), Serious Adverse Drug Reactions (SADRs) experienced by ACC study subjects in addition to assessing toxicity data reported through IND safety update reports. These evaluations allow the Committee to detect safety issues and request internal actions necessary to protect the safety of ACC subjects. Events are reported to the DSMC via Velos, the ACC Clinical Trials Management System. This data is mapped into the DSMC's custom PV database and formatted in CTCAE (all available versions) layout. Since this format and categorization is familiar, members' review of data is more efficient and clinically meaningful. The DSMC reviews

individually submitted expedited SAEs within 48 hours of submission (24 hours for any death). Committee members have access to the web-based PV system and can query the database for specific items or run the standard monthly cumulative report. The Committee looks for safety signals through patterns/trends of data reported, evaluates the signals against labeling, current knowledge and experience, and sends letters to investigators requesting additional details or explanations. The DSMC may require protocol and/or consent language changes, additional subject monitoring procedures to be put in place by the PI and discontinuation of a specific study or arm. The DSMC may share the outcome of safety reviews requiring PI action with IRB and Industry study sponsor to discuss concerns as necessary. The Committee also creates alerts for ACC investigator using this same agent or class of agents.

SAEs

The DSMC's requirements for SAE submission differs from the IRB because the goal of SAE review is different. The DSMC requires SAE submission as follows:

- **Penn Subjects (including subjects at networks, affiliates or investigator-initiated sites)**

All on-site grade 3 or higher AEs or ADRs regardless of attribution or expectedness must be submitted to the DSMC within 30 days. SAEs or SADR for Penn subjects regardless of attribution or expectedness must be submitted to the DSMC within 10 days. Reports will continue to be sent to the DSMC for 90 days following the last date the subject received study treatment/therapy or was exposed to an investigational device. All unexpected deaths or deaths related to the study agent(s)/device(s) must be reported within 24 hours. All other deaths should be reported within 30 days.

The DSMC reserves the right to modify the reporting window for certain types of studies i.e. gene therapy, adoptive therapies, Penn manufactured vaccines etc.

- **IND Safety Updates/Alerts**

IND Safety Updates/Alerts (sent by sponsors), that are specifically for the protocol open in the ACC, with a grade 3 or higher, regardless of attribution or expectedness must be submitted to the DSMC within 30 days. Events for studies using a novel agent, on any protocol in the Cancer Center, not specifically the protocol open in the ACC, should be sent within 30 days. All other IND Safety Updates/Alerts should be sent within 60 days of receipt. Once the study closes to accrual at Penn, reports should be sent to the DSMC for 30 days from the date the last Penn subject was treated. Events for studies using a novel agent or agents manufactured on campus must be sent until the protocol terminates.

Reporting Events

All events must be entered into the ACC Clinical Trials Management System (CTMS) AE/SAE form. This form was developed in Velos eResearch by the DOCM and contains all of the elements required by regulatory agencies, the DSMC and IRB for appropriate tracking and management. Entry of data into the AE/SAE form will auto populate the PV database allowing the DSMC to monitor and correlate events.

DEPARTMENT OF COMPLIANCE AND MONITORING (DOCM)

Overview of the DOCM

The DOCM operationalizes the administrative activities of the CTSRMC and DSMC, sets the standards and policies for all research operations and is also responsible for the Regulatory Affairs of the ACC.

All clinical trials approved by the CTSRMC are audited and/or monitored by the DOCM based on the risk assigned to the study and the policies of the DSMC. The purpose of these audits/monitoring visits is to evaluate protocol compliance, data integrity and to ensure that all cancer-related human subject studies are conducted in accordance with all federal (e.g. GCP, GMP, GLP, GEP, GTP, HIPAA, Part 11, FISMA etc.) and institutional policies with the goal of improving subject safety and data quality and integrity. DOCM operations, oversight and regulatory affairs activities include protocols conducted within the ACC and its extended community based practice, Pennsylvania Hematology Oncology Practices (POHA), as well as CHOP Oncology.

Auditing by Sponsor Type

The extent of monitoring/auditing conducted by the DOCM is based on the standards defined by the DSMC and the risk assigned by the CTSRMC.

- **NCI Cooperative Groups**

The DOCM 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 DOCM for review. This is referred to as “distance monitoring” since the DOCM reviews the finding and acts on any items of concern identified by the external sponsor.

- **Pharmaceutical/Biotechnical Industry**

The DOCM randomly selects industry sponsored trials for auditing. The random selection will allow for a sampling across sponsors and disease sites. Additionally, the DOCM requires the PI to provide a copy of all inspection reports conducted by the sponsor to the committee. This is referred to as “distance monitoring” since the DOCM reviews the finding and acts on any items of concern identified by the external sponsor. Industry sponsored studies using first-in-man agents are not part of the random selection process. These protocols are part of the systematic review process for high risk studies.

- **In-House/Investigator Initiated and Studies Sponsored as Other Externally Peer Reviewed**

These studies are audited by the DOCM as required by the risk level assigned by the CTSRMC. In addition to DSMC auditing, the CTSRMC may request that the DOCM provide a real-time study monitor for certain high risk in-house studies. In this case, representatives from the DOCM will meet with the study PI to establish a plan which will define the frequency and intensity of DOCM monitoring. The areas included in the plan will be inspection intervals, study aspects, regulatory documents and agent accountability (where applicable). The DOCM auditor 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.

Monitoring

Certain studies, as identified by the CTSRMC, will be monitored on an on-going basis by the DOCM. Each study will have an individualized monitoring plan developed by the DSMC and the study team. This plan must be approved by the DOCM Director. Once the CTSRMC determines that a study needs prospective monitoring, the DSMC will work with the PI and study team to develop a monitoring plan that will cover

- All of the Regulatory documentation

- Informed Consents
- Eligibility criteria
- Treatment administration and accountability
- Adverse/Serious Adverse Events and toxicities
- Response assessment
- Subject follow-up
- Data completeness
- Source documentation to Case Report Form (CRF)
- Manufacturing (where applicable)

At the conclusion of the monitoring visit, the monitor will spend time with the PI and/or study team to discuss the findings and to provide guidance on resolving deficiencies. A formal letter will be sent to the PI within about five business days. The PI does not have to respond the monitoring letter unless specifically requested to do so by the monitor. Studies that are monitored may also have periodic audits conducted by the DOCM at the discretion of the DSMC.

Distance Monitoring

The DSMC requires copies of monitoring reports/letters received from sponsored monitoring visits to be sent to the DOCM within thirty days of the visit. The DOCM requests these reports/letters to supplement routine auditing. This form of "distance monitoring" serves two key functions:

1) It alleviates the study team from duplication of effort in regards to preparation of study documents for sponsor's visits and the DOCM's. Failure to send these monitoring reports/letters inhibits the DOCM's ability judge the quality of a trial without inspecting it thus the study will be added to the schedule for routine auditing.

2) It provides the DSMC with reassurance that the trial is meeting all required standards and may result in a modification of the schedule for routine auditing. Distance monitoring does not eliminate these studies from being audited. The DSMC will focus on other types of studies first and then randomly select these types of studies.

Auditing and Monitoring Timelines

- **High risk** protocols are audited approximately six months from their first subject accrual and approximately every six month thereafter for the duration of the study. However, this schedule may be changed at the discretion of the DSMC. High enrolling or quick enrolling studies will be audited more frequently as necessary. Priority of review is given to investigator-initiated studies and non-cooperative NIH/NCI funded studies and other Externally Peer Reviewed protocols since most industry and cooperative group sponsored trials are audited on a regular basis by the sponsor. However, the DOCM 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 subjects or 10% of the total accrual, whichever is higher, are audited. A formal report is provided to the PI within about five business days 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, representatives from the DOCM acting on behalf of the DSMC meet with the PI to discuss the findings of the audit and necessary corrective actions. If the deficiencies involve subject safety or serious regulatory violations, the Cancer Center Director, DSMC Chair, and DOCM Director will meet to discuss necessary actions concerning study status.
- **Moderate risk intervention** protocols are audited approximately nine to twelve months from the first subject enrolled and annually thereafter for the duration of the study. Investigators are notified in advance of the selection of their protocol for review and cases are randomly selected. Three selected subjects or 10% of the total accrual, whichever is higher, are audited. A formal report is written to the PI within about five business days 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, representatives from the DOCM acting on behalf of the DSMC meet with the PI to discuss the findings of the audit and necessary corrective actions. If the deficiencies involve subject safety or serious regulatory violations, the Cancer Center Director, DSMC Chair, and DOCM Director will meet to discuss necessary actions concerning study status.

- **Low risk non interventional studies** are audited at approximately one year from the first subject enrolled and approximately every other year thereafter for the duration of the study. However, this schedule may be changed at the discretion of the DSMC. Investigators are notified in advance of the selection of their protocol for review and cases are randomly selected. Three selected subjects or 10% of the total accrual, whichever is higher, are audited. A formal report is written to the PI within about five business days 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, representatives from the DOCM acting on behalf of the DSMC meet with the PI to discuss the findings of the audit and necessary corrective actions. If the deficiencies involve subject safety or serious regulatory violations, the Cancer Center Director, DSMC Chair, and DOCM Director will meet to discuss necessary actions concerning study status.

Once a monitoring or audit date is selected, it can only be modified under special circumstances with the approval of the DOCM Director. Visits will not be rescheduled because the study team wants more time to organize the study. The DSMC, the University and regulatory agencies expect that studies are maintained in a high quality manner as the study progresses.

Audit Criteria and Procedures

Audits are conducted by the DOCM. Areas addressed in these audits include (not limited to):

- Regulatory documentation
 - All versions of the protocol, summary, consent, CRFs, IB etc.
 - CVs, license, Delegation of Authority, Signature logs, screening and enrollment logs
 - 1571/1572 and all relevant IND documentation
 - All IRB, CTSRMC, FDA, NCI/NIH, Sponsor, review committees, etc. correspondence including approvals and re-approvals, SAE reports, deviations
 - Agent/device accountability, shipping records, destruction
 - Training records
 - DSMB, Medical Monitor or Safety Monitoring Committee minutes
 - Monitoring Log and monitoring reports
 - Memo/Note to file
- Signed consents (study and HIPAA)
 - Originals should be available
- Eligibility criteria
 - Source documents (medical history, progress notes, imaging studies, labs, tests, concomitant medications, performance status, staging, life expectancy etc.) to verify all eligibility criteria.
- Treatment administration and accountability
 - Source documents of administration or dispensation. Administration records should contain up/down times or overall time of administration, date, dose and BSA. Agents that are dispensed in the clinic for subject self administration should be tracked via a drug diary or accounted for in the progress notes at each visit. Notes of dispensation are not sufficient to show protocol adherence/compliance.
 - Documentation of treatment modifications/holds with an explanation as to the reason.
- Adverse/Serious Adverse Events and toxicities
 - All events must have a time reference, grade, attribution, expectedness and outcome/resolution.
 - Documentation of management of events until resolution
 - Documentation of SAE reporting if not maintained in the Regulatory Binder
- Response assessment

- Tumor measurement forms, imaging, biochemical indicators and progress notes
- Adherence to RECIST criteria where applicable
- Subject follow-up
 - Documentation of follow-up visits, telephone communications, written communications (i.e. letter and e-mail)
 - Off study documentation
 - All source documentation to show full compliance with all aspects of the research protocol.
- Source documentation to Case Report Form (CRF) verification
- Overall organization and study related knowledge of staff
- Manufacturing (where applicable)

Areas Reviewed During Monitoring/Auditing Multi-Site Protocols

For investigator-initiated multi-institution studies, all of the above applies to each site participating in the study. Each site must be visited no less than once a year. Monitoring or auditing may occur by two mechanisms, electronic submissions and on-site at each location. The initial monitoring visit or audit must occur on-site and will be schedule in accordance with the DSMC's policy for high risk protocols. If minor deficiencies are identified, then the next monitoring/auditing of this site can occur via electronic monitoring of data in Velos eResearch and shipment of source documents from the site to the DOCM for data verification. Regardless of the level of deficiencies identified during this review, the next audit must be on-site. If any review reveals major deficiencies, all subsequent inspections must be on-site. Additionally, the DOCM will consult with the DSMC to determine whether or not the site should be closed.

Electronic Versions of Source Documents

If any of the above documentation is only available in electronic form, place holders should be placed in the study binder indicating where the electronic source can be located. The auditor must be notified at the time the audit is scheduled that some/all documentation is electronic. If the auditor is not informed that documents are only available electronically, s/he will not conduct an exploratory review of all the possible electronic sources to seek out missing documents. These deficiencies will be documented in the audit letter.

Audit Deficiencies and Audit Letter

Deficiencies will be recorded on the Audit Form and entered into the DSMC Tracking system. The DOCM will generate the monitoring/auditing letter and discuss concerns with the DSMC Chair prior to sending the final letter to the PI. Receipt of response letters are recorded in the DSMC Tracking System and the DOCM will follow DSMC policies for follow-up.

HIPAA

Every monitoring visit and audit includes evaluation of HIPAA compliance in accordance with the CTSRMC and IRB approved HIPAA Authorization Form. The monitor or auditor reviews the study documents to confirm that all reasonable attempts are made to protect the subject's privacy; that data has not been released to any entities other than those listed on the HIPAA Authorization form; and any data collected and released matches the data identified on the HIPAA Authorization as being authorized for such activities. All identified HIPAA deficiencies are included in the audit letter and the investigator is instructed to notify both the IRB and the University of Pennsylvania Office of Research Compliance and Integrity. The DOCM Director will work with the IRB, Office of Research Compliance and Integrity and PI to resolve all HIPAA issues.

DOCM Role in External Audits

Audits conducted by NIH/NCI, cooperative groups and/or on behalf of these groups; the FDA or any non-ACC entities are considered external audits. All contact in regards to scheduling, organization and conclusion of these audits (other than routine study specific cooperative group auditing) should

be made directly with the Director, Compliance and Monitoring. The DOCM 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 subjects. Along with organizing the study data and subjects, the DOCM will act as the liaison between the PI and the external monitoring agency.

Additional Inspections

The DOCM is responsible for annual GMP, GLP and GTP inspections of applicable on-campus facilities. Part 11 and FISMA compliance is performed on an *ad hoc* basis.

GMP

The DOCM uses the standard regulatory checklist for GMP, however, understanding that manufacturing operations in an Academic Health Center are different than facility producing commercial agents, there are areas on the checklist that are not applicable to the ACC facilities. The auditor will mark these areas with N/A.

GLP

The DOCM uses the FDA checklist for GLP, however, understanding that laboratory operations in an Academic Health Center are different than facility supporting GMP and/or conducting bioanalytical testing, there are areas on the checklist that are not applicable to the ACC facilities. The auditor will mark these areas with N/A.

GTP

The DOCM uses the FDA checklist for GTP which directly relates to preventing the introduction, transmission, or spread of communicable disease by Human Cells, Tissues, and Cellular and Tissue-Based Products (biospecimens). Manufacture, as defined in § 1271.3(e), means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging or distribution of any human cell or tissue, and the screening or testing of cell or tissue donor.

21CFR11

The DOCM conducts 21CFR11 audits as necessary. Once a system is audited and validated, it will be re-validated every two years to ensure on-going compliance. If it is determined that a system does not meet the minimum requirements for compliance, the DOCM will refer the system owner/administrator to the appropriate technical groups for assistance.

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, NCI 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. Subject safety will be monitored continuously by the PI by reviewing and documenting 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, DSMC, NCI and FDA (where applicable) 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**

CTSRMC

- All updates to study status will be immediately reported to the CTSRMC regardless of cause.
- All amendments to study documents, forms etc. 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).
- A copy of the IRB Continuing Review must be sent to the CTSRMC.
- Publications for CTSRMC approved protocols.

DSMC

- The DSMC should be immediately notified of trials terminated/suspended due to safety issues.
- Protocol exceptions requests or reports of applicable deviations should be made via our website at www.ctsrmc.org.
- Applicable AE and SAEs.
- External monitoring reports/letters
- DSMB, Medical Monitoring of Safety Monitoring Committee Reports
- Any correspondence from sponsors or regulator agencies regarding safety issues for protocols approved by the CTSRMC.

Investigators are reminded that they may delegate authority but never responsibility.

ADDITIONAL OVERSIGHT

University of Pennsylvania Human Subjects Protection Training/Certification

The University of Pennsylvania has adopted Collaborative Institutional Training Initiative (CITI) as its program for training and certification of all faculty and staff involved, on any level, in the conduct of human subjects research. The DSMC has access to the University's CITI training database and can therefore ensure that ACC staff and investigators have successfully completed the required training prior to protocol initiation.

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 protocol can receive full approval from the IRB without CTSRMC approval.**

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 subject 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

TECHNOLOGIES

Website

The CTSRMC and DSMC have developed a password protected website to give all members of the Cancer Center's research community access to guidance documents, necessary forms, electronic submissions and registrations, meeting and training calendars and ACC research blackboard. Our URL is www.ctsrmc.org. Activity of attempts to log-in, pages viewed and documents downloaded is tracked by the Database and Applications Group (DAG).

Velos

The ACC has adopted Velos eResearch as our Clinical Trials Management System (CTMS). All cancer-related protocols (not just clinical trials) and the protocol enrolled subjects must be registered in the system. Velos is only used by the ACC and content is managed and regulated by the CTSRMC and DSMC.

Velos is a full management system that includes

- Study and subject management
- Study administrative management
- Study and subject calendar creation and management
- AE/SAE management
- Financial tracking and compliance
- Development of e-CRFs

Only individuals that have received formal Velos training may access the system, regardless of their role. The ACC Velos instance is compliant with 21CFR11, which mandates training prior to any level of access. Level of access and training needs are identified by the DOCM.

Database and Application Group (DAG) Hosted Application

The ACC Database and Applications group has developed various applications and databases for the CTSRMC and DSMC to allow tracking of Committee activities and DOCM operations. The following information technologies are utilized by the CTSRMC and DSMC:

- CTSRMC Tracking Database- record, manage and report CTSRMC activities.
- CTSRMC IND Manager- creates IND submissions and ongoing data collection for follow-up reporting as required by FDA.
- DSCM Tracking Database- record, manage and report DSMC activities.
- DSMC Pharmacovigilance Database- record, manage and report events related to participation on a research protocol.
- Exception/Deviations Tracking Database- record, manage and report exceptions/deviations.

ADMINISTRATIVE INFORMATION

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:

www.fda.gov

Safety monitoring guidelines.

www.nih.gov/niams/clinical/dsmb3.html#

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

2017 Penn Tower

215-349-5238

vsallee@mail.med.upenn.edu

www.ctsrmc.org

APPENDICES

A-C, F and L-O have been removed

APPENDIX D
MULTI-SITE STUDY JUSTIFICATION

**Justification and Recommendation
for Multi-Institution Investigator-Initiated Studies
Cancer Studies
GUIDANCE**

In accordance with University of Pennsylvania policies for investigator-initiated multi-institution studies (with or without an IND), investigators conducting cancer based research outside of Penn must submit a justification form to the CTSRMC. *Note: Pennsylvania and Presbyterian Hospitals are part of Penn Medicine.*

Studies that require justification

- Therapeutic: Therapeutic intent using drugs, radiation, surgery, other biological agents, or behavioral or other interventions.
- Prevention: Modulation of cancer risk and inhibition of cancer progression using chemoprevention drugs, nutritional, dietary, behavioral, or other interventions.
- Supportive Care: Intended to improve the comfort and quality of life for the patient using drugs, nutritional, dietary, behavioral or other interventions.
- Screening, Early Detection, or Diagnostic: Directly testing the efficacy of devices, techniques, procedures; or tests for earlier or more accurate detection or diagnosis of disease.

Studies that do not require justification

- Epidemiologic, Observational, or Outcome: Studies among cancer patients and healthy populations that involve no intervention or alteration in the status of the participants, e.g., surveillance, risk assessment, outcome, environmental, and behavioral studies.
- Correlative Trial: Laboratory based studies using specimens to assess cancer risk, clinical outcomes, response to therapies, etc. Only studies that can be linked to individual patient or participant data should be reported.

Please take note of the following

- Sites that do not have their own Federal Wide Assurance are not allowed to participate.
- Private practice/community practice sites may serve as screening locations and provide standard of care but cannot participate in any experimental aspects of the study. (i.e. obtaining consent, administering study agent(s), using devices, assessing adverse events and completing protocol defined test/procedures other than ordering labs/radiology).
- Investigators without previous experience as the Principal Investigator on an investigator-initiated study must have an experienced Penn sub-investigator on the protocol.
- Investigators with previous major auditing/monitoring issues may be declined at the discretion of the DSMC.
- All non-Penn sites must complete CITI certification to document training in human subjects protection training.

**APPENDIX D
MULTI-SITE STUDY JUSTIFICATION**

**Justification for Multi-Institution Investigator-Initiated Studies
Cancer Studies**

Date	PI	UPCC#	IRB#
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Protocol Title

IND Status: PI holds IND # FDA Exemption CTSRMC Exemption

Provide justification for why you believe this study must be made available outside Penn.

Names of each institution at which you wish to conduct this study. If more than one site, provide justification for why you believe it is necessary to open this study at more than one additional site. *(attach additional sheet if necessary)*

Site Name and Location	Why selected?	Patient Population Statistics	Timeline for Opening Site	Site have own FWA?
				<input type="checkbox"/> Yes <input type="checkbox"/> No
				<input type="checkbox"/> Yes <input type="checkbox"/> No
				<input type="checkbox"/> Yes <input type="checkbox"/> No
				<input type="checkbox"/> Yes <input type="checkbox"/> No
				<input type="checkbox"/> Yes <input type="checkbox"/> No
				<input type="checkbox"/> Yes <input type="checkbox"/> No
				<input type="checkbox"/> Yes <input type="checkbox"/> No

Justification

Describe the staffing resources you have to handle this additional workload. Include details about the total number of staff that will be fully dedicated to just this study.

Describe the funding you have to cover the cost of mandatory ACC Data and Safety Monitoring Committee monitoring.

Other details you feel will help the committee

APPENDIX E
Template Monitoring Plans

MONITORING PLAN FOR IN-HOUSE STUDIES

UPCC Number

Title of Protocol

Principal Investigator

Principal Investigators acting as study sponsors are responsible for monitoring the safety of subjects 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 study.

ADDITIONAL MONITORING ENTITIES:

Note: This study will be audited by the Data and Safety Monitoring Committee in accordance with the UPCC Policy and Procedure for Auditing Clinical Protocols. Entities below are in addition to standard auditing.

Cancer Center monitoring (*Only check if advised by CTSRMC www.ctsrc.org*). A copy of the monitoring plan developed by DSMC and the study team should be attached.

Medical Monitor (MM) (*this cannot be the PI*)
This should be detailed in the study protocol. Refer to the Institutional DSMP for details.

Safety Monitoring Committee (SMC)
This should be detailed in the study protocol. Refer to the Institutional DSMP for details.

Data Safety Monitoring Board (DSMB)
This should be detailed in the study protocol. Refer to the Institutional DSMP for details.

EVALUATING ADVERSE EVENTS:

During the course of the study, safety will be monitored on an ongoing basis by the Investigator(s) and the study team. The Investigator(s) will review the study charts to evaluate Adverse Events (AEs) **every study calendar day or visit** and document the grade, relationship to the study agent/device/procedure, expectedness and the course of action for the subject(s).

PI initials

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, grading criteria and grading exceptions for this study must be documented in the SAE section of the study protocol.

APPENDIX E
Template Monitoring Plans

MONITORING PLAN FOR IN-HOUSE STUDIES

UPCC Number

Title of Protocol

Principal Investigator

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 at least every 30 days.

PI initials

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

- FDA
- NCI/NIH
- IRB
- DSMC (via website, www.ctsrmc.org)
- Medical Monitor
- Safety Monitoring Committee
- Data Safety Monitoring Board (DSMB)

LABORATORY DATA QUALITY

Lab results for each subject will be reviewed on an **ongoing basis** and the review will be documented by initialing and dating the lab report(s) or describing the review in the relevant progress notes.

PI initials

PI Signature

Date

APPENDIX E
Template Monitoring Plans

MONITORING PLAN FOR INDUSTRIAL OR COOPERATIVE GROUP SPONSORED STUDIES

UPCC/Coop Number

Title of Protocol

Principal Investigator

Sponsor

Principal Investigators are responsible for monitoring the safety of subjects 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.

Note: This study will be audited by the Data and Safety Monitoring Committee in accordance with the UPCC Policy and Procedure for Auditing Clinical Protocols. Entities below are in addition to standard auditing.

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 monitoring (*Only check if advised by CTSRMC www.ctsrcmc.org*). A copy of the monitoring plan developed by DSMC and the study team should be attached.
- Medical Monitor (MM)
- Safety Monitoring Committee (SMC)
- Data Safety Monitoring Board (DSMB)

The corresponding study protocol **must** provided details regarding how monitoring will be performed, the frequency of monitoring and items that will be reviewed.

SAEs REPORTING AND TRACKING

PI will report SAEs to: *(check all that apply)*

- Sponsor
- CRO
- FDA
- NCI/NIH
- IRB (*only per SOP 404*)
- DSMC
- Medical Monitor
- Safety Monitoring Committee (SMC)
- Data Safety Monitoring Board (DSMB)

The PI is responsible for making sure all sponsors are aware of the Penn IRB's policy for reporting and acknowledging IND Safety Updates/Off-site SAEs. **SOP 404 (June 03, 2007)**

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 at least every 30 days.

PI initials

APPENDIX E
Template Monitoring Plans

MONITORING PLAN FOR INDUSTRIAL OR COOPERATIVE GROUP SPONSORED STUDIES

UPCC/Coop Number

Title of Protocol

Principal Investigator

Sponsor

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

- Sponsor
- CRO
- NCI/NIH
- IRB
- DSMC (via website, www.ctsrmc.org)
- Medical Monitor
- Safety Monitoring Committee
- Data Safety Monitoring Board (DSMB)

LABORATORY DATA QUALITY

Lab results for each subject will be reviewed on an **ongoing basis** and the review will be documented by initialing and dating the lab report(s) or describing the review in the relevant progress notes.

PI initials

PI Signature

Date

APPENDIX G
IND Exemption Determination Form

Determination of the Need for an IND in Cancer Studies

Submit the completed form with a copy of either the protocol or protocol summary, and any applicable FDA package inserts, to CTSRMC at the address, fax or email noted below. You will be contacted with a recommendation as to whether or not the noted study qualifies for an IND exemption.

The definition of a new drug is as follows:

A NEW DRUG IS:

“...Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs [i.e. the FDA], as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, ...” [21 USC 321]

Examples of therapies typically requiring an IND (i.e. **not** exempt from the IND process):

- Any agent not approved by the FDA
- Agents approved by the FDA, but studied for a different indication

Directions for completing the form:

1. Please complete information on the attached form in sections marked with gray text areas or gray check boxes. Where applicable, you may respond to by providing an abbreviated answer and referencing supporting sections of the FDA approved labeling. In these cases please use any combination of highlighters, footnotes and direct annotations on the attachments to the specific sections of the labeling you are referencing.
2. Make sure the date field is completed with the date of the form submission.
3. Attach a copy of the study protocol or protocol summary and any supporting documents (i.e. FDA approved labeling where applicable).
4. Print a copy or save an electronic copy for your records
5. Send the completed form and applicable additional information to:

If sending hard copy fax to:

215-662-2139

If sending an electronic copy, email to:

janine.koury@uphs.upenn.edu

Please feel free to contact CTSRMC with any questions you may have with the above information or the attached form.

APPENDIX G

IND Exemption Information Form

General Information

Date

Investigator name:	Primary contact if other than Investigator:
Investigator information	Primary contact information (if other than investigator)
Phone:	Phone:
Pager:	Pager:
Email:	Email:
Proposed Study Title	

Study Drug/Treatment Information

Planned Investigational Use	<u>FDA-Approved Use</u>
<p>1. Study drug/treatment Generic name: Commercial name:</p> <p><u>Please complete for additional study agents.</u></p> <p>2. Study drug/treatment Generic name: Commercial name:</p> <p>3. Study drug/treatment Generic name: Commercial name:</p>	<p>1. Is this drug/treatment FDA approved? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>1a. Is this drug/treatment FDA approved to treat cancer? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>2. Is this drug/treatment FDA approved? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>2a. Is this drug/treatment FDA approved to treat cancer? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>3. Is this drug/treatment FDA approved? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>3a. Is this drug/treatment FDA approved to treat cancer? <input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>1. Indication</p> <p>2. Indication</p> <p>3. Indication</p>	<p>1. Approved Indication</p> <p>2. Approved Indication</p> <p>3. Approved Indication</p>

apply) <input type="checkbox"/> Oral Subcutaneous <input type="checkbox"/> <input type="checkbox"/> Intravenous <input type="checkbox"/> Cutaneous <input type="checkbox"/> Intramuscular <input type="checkbox"/> Ocular <input type="checkbox"/> Other (Please list):	<input type="checkbox"/> Intravenous <input type="checkbox"/> Cutaneous <input type="checkbox"/> Intramuscular <input type="checkbox"/> Ocular <input type="checkbox"/> Other (Please list):
1. Dosing regimen: 2. Dosing regimen: 3. Dosing regimen:	1. Approved Dosing regimen: 2. Approved Dosing regimen: 3. Approved Dosing regimen:

Study Questions

<ul style="list-style-type: none"> Does the study require any change in the approved formulation (e.g. over encapsulating, adding of additional substances or components to facilitate study blind, crushing or suspension of dry drug, etc.)? 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Are there other FDA-approved drugs/treatments for the condition you plan to study? If yes, please list AND attach the FDA approved labeling for these other drugs/treatments: 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Funding source for this study: 	
<ul style="list-style-type: none"> Are your or the funding source intending to use study data or results to accomplish either of the following? <ul style="list-style-type: none"> • Support an indication for the study drug/treatment • Support a marketing claim or application 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Does the planned use of the study drug(s)/treatment(s) represent an increased risk to subjects being studied? Please list rationale for either decision. 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Is there sufficient clinical experience described in the literature to determine the study drug/treatment is safe? 	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>Note For Cancer Treatment Only: When the regimen described in the literature does not use exactly the doses planned for study, incremental differences in doses from those described in the literature would not normally pose a</p>	

significant risk.

Please provide references.

- What is the risk to subjects if the study drug/treatment is not effective?

APPENDIX H

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

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

- *An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.*

Adverse Drug Reaction (ADR)

In the **pre-approval** clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established:

- *All noxious and unintended responses to a medicinal product related to any dose should be considered Adverse Drug Reactions.*

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Marketed medicinal products, a well-accepted definition of an adverse drug reaction in the post-marketing setting is

- *A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.*

The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavorable) effects, but also positive (favorable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

Unexpected Adverse Drug Reaction (UADR)

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product or labeling for marketed products)

NOTE: Please refer to the CTEP Comprehensive Adverse Event and Potential Risks (CAEPR) and Agent Specific Adverse Event List (ASAEL) for additional details on expectedness.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf

Serious Adverse Event (SAE)

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it **does not refer to an event which hypothetically might have caused death if it were more severe.**

- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other

outcomes listed in the definition above. These should also usually be considered serious. Other kinds of events can be labeled “serious adverse events” at the discretion of the investigator.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe." which are not synonymous, the following note of clarification is provided: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Severity Grading Scale for Adverse Events

Many disease specific groups have developed toxicity grading scales. For example, most cancer clinical trials use the Common Terminology Criteria for Adverse Events (CTCAE) developed by the NCI. The CTCAE 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”.

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.

Adverse Event Attribution Categories:

- Unrelated- The AE is clearly NOT related to the intervention
- Unlikely- The AE is doubtfully related to the intervention
- Possible- The AE may be related to the intervention
- Probable- The AE is likely related to the intervention
- Definite- The AE is clearly related to the intervention

Expedited Adverse Event Reporting Requirements

The reporting requirements and timing of reporting are dependent on the regulatory status of the study, 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>. (*Tables 1 and 2 below*).

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

CDUS Guidelines for Routine Adverse Event Reporting on Trials using Agent(s) under a CTEP IND

Attribution	Adverse Event				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			CDUS	CDUS	CDUS
Unlikely			CDUS	CDUS	CDUS
Possible	CDUS	CDUS	CDUS	CDUS	CDUS
Probable	CDUS	CDUS	CDUS	CDUS	CDUS
Definite	CDUS	CDUS	CDUS	CDUS	CDUS

The CTMS is the non-Governmental organization contracted by CTEP to receive, review and perform data management tasks on individual patient case report forms for Phase 1 investigational agent studies designated for CTMS data reporting.

CTMS Guidelines for Routine Adverse Event Reporting for Trials using Agent(s) under a CTEP IND

Attribution	Adverse Event				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	CTMS	CTMS	CTMS	CTMS	CTMS
Unlikely	CTMS	CTMS	CTMS	CTMS	CTMS
Possible	CTMS	CTMS	CTMS	CTMS	CTMS
Probable	CTMS	CTMS	CTMS	CTMS	CTMS
Definite	CTMS	CTMS	CTMS	CTMS	CTMS

Expedited Adverse Event Reporting

Adverse Event Expedited Reporting System (AdEERS)

CTEP's original web-based system for electronic submission of expedited reports on protocols utilizing a CTEP sponsored IND was published in 1998. The current version of AdEERS provides pathways for all Cooperative Group protocols including commercial agent-only; radiation-only; surgery-only; device-only; all combinations. An expedited AE report for all protocols utilizing agents under a CTEP IND must be submitted electronically to CTEP via AdEERS.

In the rare event when Internet connectivity is disrupted, a report may be submitted using the Adverse Event Expedited Report – Single Agent or Multiple Agents paper template (available on the CTEP Home Page at <http://ctep.cancer.gov>).

Templates must be faxed to CTEP at 301-230-0159.

When Internet connectivity is restored, a report submitted on a paper template must be entered into electronic AdEERS by the original submitter of the report at the site. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

All AEs reported via AdEERS must also be reported via the routine AEs reporting defined by the protocol.

All Cooperative Groups trials must use AdEERS for expedited reporting of AEs resulting from:

- Trials utilizing a commercial agent only;
- Trials utilizing an investigational agent under a CTEP IND and a commercial agent on separate arms;
- Trials utilizing an investigational agent under a CTEP IND and a commercial agent on the same arm.

Expedited Adverse Event Reporting of Hospitalization or Prolongation of Existing Hospitalization for all Phases of Trials

CTEP defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should be reserved for situations where the adverse event truly fits this definition and not for hospitalizations associated with less serious events. For example, a hospital visit where a patient is admitted for observation or minor treatment (e.g., hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling, is not an AE, and therefore is not to be reported either as a routine AE or in an expedited report.

Hospitalization or prolongation of hospitalization associated with Grade 3 events, unexpected and expected, and regardless of attribution; require expedited reporting for trials utilizing an agent under a CTEP IND.

24-Hour Notification for CTEP IND Trials

The adverse event 24-hour notification requirement provides an early detection system for potential safety problems. Adverse events that must be reported within 24-hours of learning of the event are dependent upon the phase of trial, the agent/intervention (investigational or commercial), whether the event is expected or unexpected, the grade and attribution. Table C and Table D outline 24-hour notification to CTEP for AEs that occur on trials utilizing an agent under a CTEP IND.

Adverse events that fulfill the 24-hour reporting requirement must be reported electronically via AdEERS at <http://ctep.cancer.gov>.

To ensure vigilance for AEs that require 24-hour notification, AdEERS is programmed to facilitate complete, timely submission. Initiation of an AdEERS report via the 24-Hour Pathway generates these events:

When the Reporter Information screen is saved, an e-mail is submitted to the Reporter indicating the initiation of an AdEERS report.

- Submission of a 24-hour notification is only the beginning of the requirement for a complete AdEERS report, and the 5-day clock commences. The complete report must be submitted to CTEP, NCI within 5 calendar days.
- On calendar day 3, if the complete report has not been submitted, a system-generated email is sent to the Reporter, to the local treating physician, to the Study PI, and to the Lead Group Coordinator (where applicable). The message is a reminder that the complete report associated with a 24-hour notification is due in 2 calendar days.
- On calendar day 6, if the complete report has not been submitted, a system-generated email is sent to the Reporter, to the local treating physician, to the Study PI, and to the Lead Group Coordinator (where applicable) This second message reminds recipients that the complete report associated with a 24-hour notification is overdue.
- On calendar day 8, if the complete report has not been submitted, a final email is sent to the Reporter, to the local treating physician, to the Study PI, to the Lead Group Coordinator (where applicable) and to CTEP. Personal correspondence from CTEP will follow. The incomplete report initiated by a 24-hour

notification will be flagged by the system as 'Initiated, not submitted', and although no longer accessible in the system, it is available for audit purposes.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to CTEP by telephone at 301-897-7497.

24-Hour Notification for non-CTEP IND Trials

Cooperative Groups have the option to use the AdEERS 24-Hour pathway for all Group trials. However, 24-hour notifications for non-CTEP IND trials will go only to the Lead Group Coordinator, not to CTEP, NCI. The automatic electronic reminders are not operative in the 24-hour pathway for non-CTEP IND trials. To avoid congestion of the AdEERS system, incomplete non-CTEP IND reports initiated with a 24-hour notification will be withdrawn on calendar day 8.

Routine and Expedited Reporting Requirements for Specialized Adverse Events: Reporting Requirements for Baseline Adverse Events

Although a pertinent positive finding identified on baseline assessment is not an 'AE,' when possible it is to be documented as 'Course Zero' using CTC/CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the trial and reported if it fulfills expedited AE reporting guidelines.

- If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required (assign attribution and refer to Table C or Table D).
- If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required (assign attribution and refer to Table C or Table D).
- No modification in grading is to be made to account for abnormalities existing at baseline.

Reporting Requirements for Persistent/Recurring Adverse Events

Persistent Adverse Events: A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

Routine reporting: The event must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

Expedited reporting: The event must be reported only once unless the grade becomes more severe in the same or a subsequent course.

Recurring Adverse Events: A recurring AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

Routine Reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.

Expedited Reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require AdEERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

IMPORTANT: An expedited report (AdEERS) is required for Grade 3 or higher AEs with hospitalization or prolongation of hospitalization at any time, regardless of persistent/recurring AEs.

Reporting Requirements for Adverse Events experienced in a Clinical Trial utilizing Investigational Agent(s) and Commercial Agent(s) on Separate Arms under a CTEP IND

Routine Reports : Routine AE reporting for Phase 1 and Phase 2 clinical trials using an investigational agent and a commercial agent on separate arms is via either CTMS or CDUS as stated in the protocol.

Routine AE reporting for Phase 3 clinical trials using an investigational agent and a commercial agent on separate arms must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators.

Expedited Reports: An event that occurs on an arm using an investigational agent (agent under an IND) must be assessed in accordance with the guidelines for investigational agents in Table C and Table D, and where indicated, an AdEERS report must be submitted.

An event that occurs on an arm using a commercial agent must be assessed as specified in the protocol. In general, only Grade 4 and 5 events that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to each protocol for specific AE reporting requirements or exceptions.

Commercial agent expedited reports must be submitted by the Cooperative Group to the FDA via AdEERS. In general, only Grade 4 and 5 events that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to each protocol for specific AE reporting requirements or exceptions. AdEERS is programmed to automatically submit the report to FDA. CTEP does not review commercial agent only expedited reports.

Reporting Requirements for Adverse Events experienced in a Clinical Trial utilizing Investigational Agents in combination with Commercial Agent(s) on the same arm

NOTE: The combination of an investigational agent with a commercial agent under a CTEP IND is considered investigational.

Routine Reports- Routine AE reporting for Phase 1 and Phase 2 clinical trials using an investigational agent in combination with a commercial agent is via either CTMS or CDUS as stated in the protocol.

Routine AE reporting for Phase 3 clinical trials using an investigational agent and a commercial agent in combination must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators

Expedited Reports- An event that occurs on a combination trial must be assessed in accordance with the guidelines for investigational agents in Table C and Table D, and where indicated, an AdEERS report must be submitted.

An event that occurs prior to administration of the investigational agent must be assessed as specified in the protocol. In general, only Grade 4 and 5 events that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to each protocol for specific AE reporting requirements or exceptions.

Commercial agent expedited reports must be submitted by the Cooperative Group to the FDA via AdEERS.

An investigational agent might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected event (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

TRIALS UTILIZING AN AGENT UNDER A CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events Based on Phase of Trial

Phase 1 Trials utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that occur within 30 Days of the Last Dose of the Investigational Agent

Table C: Reporting Requirements for Adverse Events that occur within 30 Days¹ of the Last Dose of the Investigational Agent on Phase 1 Trials

	1	2	2	3	3	4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization without Hospitalization	Expected with Hospitalization without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days Not Required	10 Calendar Days Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days 24-Hour; 5 Calendar Days	10 Calendar Days Not Required	24-Hour; 5 Calendar Days

¹Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows: AdEERS 24-hour notification followed by complete report within 5 calendar days for: Grade 3 unexpected events with hospitalization or prolongation of hospitalization Grade 4 unexpected events Grade 5 expected and unexpected events ²Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Phase 2 and Phase 3 Trials utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that occur within 30 Days of the Last Dose of the Investigational Agent

Table D: Reporting Requirements for Adverse Events that occur within 30 Days¹ of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

	1	2	2	3	3	4 & 5	4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization without Hospitalization	Expected with Hospitalization without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days Not Required	10 Calendar Days Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days 10 Calendar Days	10 Calendar Days Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

¹Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows: AdEERS 24-hour notification followed by complete report within 5 calendar days for: Grade 4 and Grade 5 unexpected events AdEERS 10 calendar day report: Grade 3 unexpected events with hospitalization or prolongation of hospitalization Grade 5 expected events ²Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Exceptions for Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures must be specified in the text of the protocol. The protocol specific guidelines supersede the CTEP, NCI Adverse Event Reporting Guidelines (Table C and Table D) for AE reporting.

Persistent or Significant Disabilities/Incapacities

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies or birth defects, must be reported via AdEERS if they occur at any time following treatment with an agent under a CTEP IND.

Death

Death occurring after the last dose of an agent under a CTEP IND agent must be submitted via AdEERS within the timelines outlined in Table C and Table D.

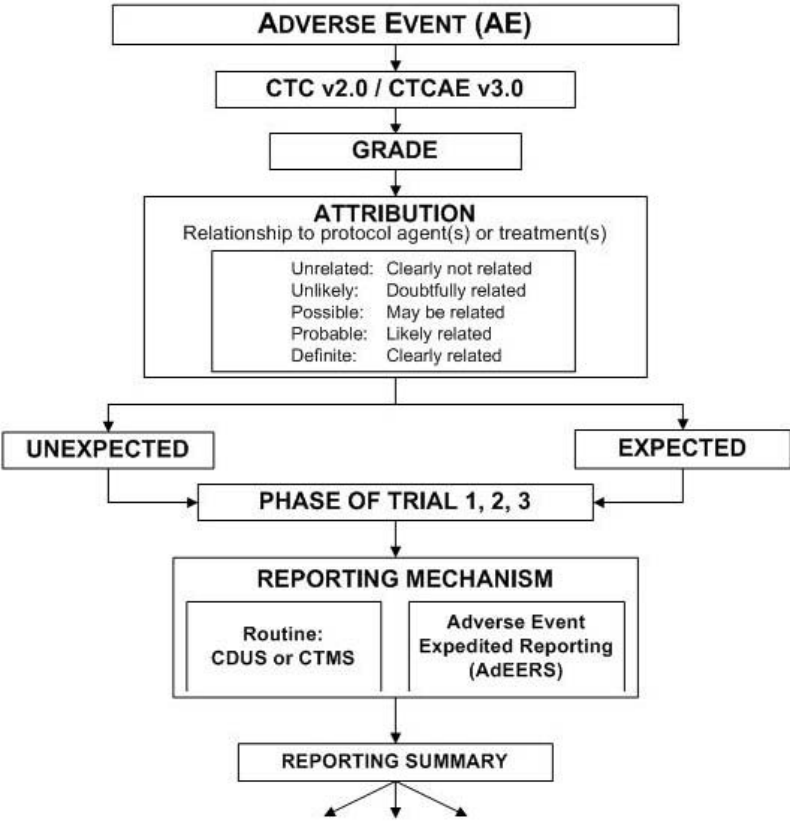
- Any death occurring within 30 days of the last dose, regardless of attribution to an agent under a CTEP IND.

IMPORTANT: An AdEERS 24-hour notification is not required for death clearly related to progressive disease.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent under a CTEP IND.

THE ADVERSE EVENT REPORTING REQUIREMENT PARADIGM FOR AGENTS UNDER A CTEP IND

The following describes the process for determining if an adverse event is reportable to CTEP, NCI.



ATTRIBUTION	GRADE 1		GRADE 2		GRADE 3		GRADE 4		GRADE 5	
	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED	UNEXPECTED	EXPECTED
UNRELATED	CTMS	CTMS	CTMS	CTMS	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
UNLIKELY	CTMS	CTMS	CTMS	CTMS	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
POSSIBLE	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
PROBABLE	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
DEFINITE	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS

CDUS – CLINICAL DATA UPDATE SYSTEM for Routine Reporting CTMS – CLINICAL TRIALS MONITORING SERVICE for Routine Reporting AdEERS – EXPEDITED REPORTING (This includes hospitalization [or prolongation of existing hospitalization] for any event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization regardless of requirements for Phase of study, expected or unexpected, and attribution.)

FDA Requirements for IND holders

A sponsor-investigator holding an IND should notify FDA via an IND Safety Update of any adverse event associated with the use of the drug that is BOTH serious AND unexpected; or any findings in laboratory animals that suggests a significant risk for human subjects including mutagenicity, teratogenicity or carcinogenicity. The sponsor-investigator holding an IND should also notify FDA by telephone or fax of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than seven calendar days after the initial receipt of the information.

FDA Mandatory Reporting (3500A) Timelines

- 5-day: As specified in the device regulations, for reports of adverse events that necessitate remedial action to prevent an unreasonable risk of substantial harm to the public health, or are required by FDA by written notice.
- 7-day: As specified in 21 CFR 606.170(b), blood collection or blood transfusion fatalities should be reported within 7 days of the fatality.
- 10-day: As specified in the device regulations, for adverse event reports of death and serious injury from user facilities.
- 15-day: As specified in the drug and biologic, including human cell, tissue, and cellular and tissue-based product (HCT/P) regulations, for reports of serious and unexpected adverse events.
- 30-day: As specified in device regulations, for initial reports of a device that may have caused or contributed to a death or serious injury or for a device malfunction that would be likely to contribute to a death or serious injury if it were to recur.
- Periodic: As specified in the drug and biologic regulations, for reports of serious labeled and non-serious (labeled and unlabeled) adverse events.
- Initial: Check if the report is the first submission of a manufacturer report. For devices, this is the 30-day report.
- Follow-up: Check if the report is a follow-up to a previously submitted report.
 - Follow-up reports on devices should not repeat material that was submitted in the initial report, but should only provide additional or corrected information on the previously reported event. Follow-up reports on drugs and biologics, including HCT/Ps, should contain information that was submitted in the original report if the information is still correct.
 - If a follow-up report, make sure that the manufacturer report number for the previously submitted initial report is recorded in block G9. In the blank provided in block G7 after follow-up, record the appropriate sequence of follow-up to that particular initial report (e.g., first follow-up report=follow-up #1, second follow-up report=follow-up #2, and so on).
 - For drug and biologic, including HCT/P manufacturers: If submitting a follow-up to a report originally obtained from FDA through a MedWatch to Manufacturer program transmission of a

serious direct report, check the other box in block G3 and enter the FDA-assigned report number there.

<http://www.fda.gov/Safety/MedWatch/default.htm> ,
<http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149238.htm> or the CTSRMC website www.ctsrc.org. The MedWatch form can be sent the following ways online, by mail or fax. MedWatch 5600 Fishers Lane Rockville, Maryland 20852-9787. Fax at 1-800-332-0178.

Investigations involving gene therapy and cellular products

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm>).

APPENDIX I MULTI-SITE MANUAL OF PROCEDURES TEMPLATE

Manual of Procedures (MOP) Content for Abramson Cancer Center Investigator-Initiated Multi-Site Trials

PURPOSE:

All Penn instantiated Multi-Site (Multi-Institutional) studies must have a study specific MOP to direct each site's conduct of the study. The purpose of this document is to provide full instructions to each site on how the protocol should be conducted, expectations of each site, key contacts etc. This manual also guides the Penn Investigator and his/her study team on the daily expectations of study conduct including administration, organization, operations, corrective actions, interaction and communication. The level of detail is much greater than the study protocol. The MOP should be written using step-wise specific language and details. Generalizations are not appropriate for this type of document. You are writing a manual, not simply responding to the prompts below. Think of the MOP as a "User's Manual"-- for all users.

HINT: You know you have a well written and designed MOP when a site can almost fully conduct the study by reading only the protocol and MOP.

Please note: The outline below is a guidance template to provide you with a list of sections and hints of what should be include in each section of the Manual of Procedures. Each study's manual will be different and may require more sections than the outline below.

Prior to receiving full CTSRMC approval to open a Multi-Site study, the CTSRMC must approve the **Justification** then the study specific MOP must be approved by the Data and Safety Monitoring Committee (DSMC).

Below are the areas that **minimally** must be address in the study specific MOP. Additional details may be required at the discretion of the DSMC.

Note: The Penn PI cannot delegate any of his/her sponsor authorities or responsibilities to other sites.

12. List locations (with address, phone number, fax number and e-mail) of each proposed site, each site investigator. Provide copies of their CVs and proof of training in Human Subject's Research Protection.
13. Provide a description of how each site will be initiated. Details of in-service training with all site staff (i.e. investigators, coordinators/nurses, data managers, pharmacists and any other study personnel) is required. Total In-service training cannot be conducted remotely. Creation and maintenance of initiation documentation must be included.
14. Provide a description of how eligibility will be confirmed by the coordinating (primary) site **prior** to enrolling each subject on the trial.
15. Provide a description of how IRB approval, amendments, SAEs, annual review etc. will be tracked by your group for each site.
16. Provide a description of how key data (identify the data and the importance) will be submitted to the coordinating (primary) site in a manner that will allow you to track progress in a meaningful way and additionally cut down on potential errors/deviations/violations.
17. Provide a description of the deviation process. Who will be notified, within what time frame and who will ultimately grant approval. Details should include the contact's name, title, address, phone number, fax number and e-mail. **Deviations from eligibility are not acceptable under any condition.**

18. Provide a description of Serious Adverse Event (SAE) reporting and tracking for each site. Identify how events will be reported to the coordinating (primary) site, the timelines for reporting, who the events should be reported to (name, title, phone number, fax number and e-mail), who will report the off-site SAEs to applicable entities (e.g. Penn IRB, DSMC, other sites participating in the study, NCI and/or FDA) and how the coordinating (primary) site will document, report and follow-up off-site SAE reports.
19. Provide a description of how the coordinating (primary) site will monitor study progress on an on-going basis. In addition, details should be provided to explain the role the DSMC will play in prospective monitoring and periodic auditing. **If you are not contracting with an approved vendor for these services, you must have funding to support DSMC monitoring/auditing of each site.** Describe how data from the external site(s) will be made available in between on-site visits to the DSMC if requested for QA/QC purposes. ***You must contact the DSMC to work out the financial details prior to formulating this section.***
20. Provide a description of the corrective action plan for issues such as the following: for example, if a subject is enrolled without approval from the coordinating (primary) site, how will this be handled, who will do it and within what time frame? If a site does not submit data in accordance with the timeline identified, how will this be handled and in what time frame? Address all of the key areas that could result in the need for exceptions or deviations.
21. Describe how treatment administration will be monitored and how study agent(s) or devices will be accounted for at each site.
15. Describe the process for monitoring study progress via pre-scheduled conference calls/meeting to update all sites on progress/issues, resolve problems etc. The timeline described in the plan must be agreed to by all parties and meetings documented with minutes. For example, if it is agreed to have a call with the PIs and coordinators monthly, minutes must be documented to show that these meetings occurred, action items were addressed etc.
16. A Remote Data Capture (RDC) system to collect protocol data is mandatory and **must be done using ACC's CTMS Velos e-Research**. Provide a description of the system including:
 - a. Identifying the database being used for data storage
 - b. Identifying the application used to develop user interface
 - c. Describing how the system was tested and validated for HIPAA and 21CFR11 compliance
 - d. Describing how the system is accessed (web or desktop installed application). If desktop installed how does this occur (remotely, locally etc.)
 - e. Explain who is managing the system and how bug and upgrades are handled
 - f. Detail where the data will be stored (i.e. local server, remote data warehouse, on your desktop etc.)
 - g. Note if the application is on the same server or a different location than the database. If different, describe how they will securely communicate
 - h. Identify who will "own" the data
 - i. Explain how access will be restricted to only relevant users
 - j. Provide the frequency of data syncs (if applicable)
 - k. Describe how end user training will be conducted
 - l. Identify which PHI be collected and stored and the encryption process to protect this critical data
 - m. Explain how data will be queried and cleaned,
 - n. Detail who has access to the hardware used to store the data, who has access to the application that collects the data and who has access to the raw data
 - o. Describe how batch data loading will occur (if any)

- p. Describe any interfaces/portals that have been developed for communication with other systems
 - q. Provide details about back-up, long term storage and disaster recovery
 - r. Explain if this system will be considered the original electronic source or will the paper documents serve as the original source and the RDC system considered an analysis tool.
- 17. Describe how early termination (due to safety issues, lack of efficacy, agent/device availability etc.) of the study at the sites will be handled.
 - 18. Describe how the site will be "closed out".
 - 19. Describe how e-CRFs will be reviewed and queried for data accuracy and completeness.

Each site must be trained on the MOP and maintain a copy in each site's regulatory binder. [Once the MOP is approved, all amendments must be approved by the DSMC.](#)

**APPENDIX J
DEVIATION LOG EXAMPLE**

Incidental Study Deviations Log- BY PROTOCOL
Protocol *Number*
Protocol *Name*

NOTE: Deviations from eligibility, stopping rules, study agent dose modifications, changes in device usage or others deviations that may impact subject safety or outcome analysis must be formally documented and reported, not logged.

Date	Subject ID and Initials	Timing	Type	Details (<i>attach additional reports/documents if appropriate</i>)	PI Signature and Date
		<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:					
		<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:					
		<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:					
		<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:					
		<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:					
		<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:					
		<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		

APPENDIX J
DEVIATION LOG EXAMPLES

Incidental Study Deviations Log- BY SUBJECT

Protocol *Number*

Protocol *Name*

Subject *ID#*

Subject *Initials*

NOTE: Deviations from eligibility, stopping rules, study agent dose modifications, changes in device usage or others deviations that may impact subject safety or outcome analysis must be formally documented and reported, not logged.

Date	Timing	Type	Details (<i>attach additional reports/documents if appropriate</i>)	PI Signature and Date
	<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:				
	<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:				
	<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:				
	<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:				
	<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:				
	<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:				
	<input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective	<input type="checkbox"/> Missed Dose <input type="checkbox"/> Missed Lab/Test <input type="checkbox"/> Missed Visit <input type="checkbox"/> Other (<i>detail</i>)		
Comments:				

APPENDIX K 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 must include investigators outside of the University of Pennsylvania. Internal members may be used for specialized expertise (if necessary).
- 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 subject 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.

APPENDIX K

Guidelines Regarding Data Safety Monitoring Board (DSMB)

- 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 subject 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 subject 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.

APPENDIX K

Guidelines Regarding Data Safety Monitoring Board (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.