

Abramson Cancer Center of the University of Pennsylvania

Institutional Data and Safety Monitoring Plan (DSMP)

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TABLE OF CONTENTS

SECTIONS	PAGE
Introduction	4
Institutional and Study Specific Monitoring Plan	4
Principles Used to Guide the Development of the ACC Institutional DSMP	4
Auditing versus Monitoring	4-5
Acc Risk Categories For Studies	5
Clinical Trials Scientific Review And Monitoring Committee (CTSRMC)	6-17
Data And Safety Monitoring Committee (Dsmc)	18-26
Department Of Operations, Compliance And Monitoring (DOCM)	27-34
Responsibilities Of The Principal Investigator (Pi)	35
Additional Oversight	35-36
Technologies	36
Forms and Guidance	36
Administrative Details	36
Further Guidance	36



A Cancer Center Designated by the
National Cancer Institute



Introduction

The Abramson Cancer Center (ACC) of the University of Pennsylvania places the highest priority on ensuring the safety of subjects participating in human subjects research and protecting the quality and integrity of study data, outcomes and endpoints. 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 both investigator and Cancer Center monitoring, auditing and oversight of studies conducted as part of the ACC which includes The Children's Hospital of Philadelphia (CHOP) Center for Childhood Cancer Research.

The ACC established a comprehensive Quality Control (QC), Quality Assurance (QA), Regulatory Affairs (RA) and Pharmacovigilance (PV) system for all cancer based human subject research in September 2001 and this system has continued to evolve to fit the requirements of NCI, FDA, HHS 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 Operations, Compliance and Monitoring (DOCM).

Institutional and Study Specific Monitoring Plans

This Institutional DSMP details the ACC wide policies, procedures and best practices concerning study and regulatory compliance and also provides guidance to all faculty and staff involved in cancer research on the development and implementation of their own study-specific Monitoring Plan which serves as the quality control and assurance plan for their studies.

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. Per the NIH, the oversight plan should be commensurate with the risks identified for each specific study. 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 or auditing must be.
2. As the intensity of auditing must be proportionate to risk, some effort must be made to characterize the risk. Study complexity is the foundation the definition of risk. Factors that impact complexity and therefore must be considered in assessing and assigning a DOCM oversight risk category include: risk inherent to the population being studied; risk associated with the intervention or treatment; study involves an IND or a medical device (IDE) held by ACC investigators, study intends to enroll vulnerable populations; involves complicated dosing schemes; involves dose escalation/de-escalation, phase of study, whether a study is in-house or investigator-initiated, whether a study is an investigator-initiated multi-center, the experience of the research team with the agent and/or populations; experience nationally/internationally with the agent/device, prior audit outcomes of the investigator; monitoring and/or auditing by non ACC DOCM staff; conflict of interest, and special circumstances as determined by the CTSRMC and/or DSMC.
3. The methods and degree of compliance oversight that must be conducted for cancer-related research protocols is commensurate with the type of study and level of risk as assigned by the CTSRMC at the time of initial approval. There are a number of options for overseeing protocols depending upon the complexity, risks, and nature of the protocol. **Risk specifically identifies the depth and level of auditing required by ACC DOCM auditors.** Table 1 summarizes the risk categories for auditing purposes.

Auditing and Monitoring

The ICH defines auditing as: *"A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."*

The ICH defines monitoring as: *"The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."*

Based on these definitions, the ACC DOCM provides oversight through auditing and the study PI conducts oversight through monitoring. The CTSRMC requires protocol submissions to include a PI Monitoring Plan (MP) that must be followed for the duration of the study by the study team. This plan should complement any plans developed by study sponsors (where applicable) and must be via one of the templates developed by the DOCM. The purpose of a MP is to assure that each study has a plan in place to oversee the safety of the subjects and the validity and integrity of the data on an ongoing 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.

TABLE 1: ACC Audit Risk Categories

No Risk	Low Risk	Moderate Risk	High Risk*
<ul style="list-style-type: none"> • Biospecimen collection/banking • Residual collecting • Retrospective chart reviews • De-identified genetics studies • Survey/Questionnaire • HUD protocols 	<ul style="list-style-type: none"> • Study poses limited risk compared to that experienced in daily life (e.g. blood draw, physical exam, psychological testing). • Studies using healthy human subjects and the population sciences, e.g., observational, behavioral and epidemiologic studies. • Interventional studies not intended to treat cancer or conditions related to a cancer diagnosis. • Nutrition studies not including dietary supplements • Exercise studies • Pharmaceutical/Biotechnology sponsored research. • Studies for which the University or any School within the University serves as the sponsor. • Any study for which the University or any School within the University manages the IND/IDE 	<ul style="list-style-type: none"> • Nutrition studies using dietary supplements • Identified genetics studies • Involves a procedure with greater than minimal risk compared to that experienced in daily life (e.g. research biopsies, imaging with exposure greater than routine care, acupuncture/pressure, etc.) • Any study that is monitored and/or audited by entities outside of the ACC DOCM. 	<ul style="list-style-type: none"> • Any in-house or investigator-initiated cancer treatment trial (with or without a faculty held IND/IDE) that is NOT monitored or audited by entities outside of the ACC • Any interventional study that uses agents manufactured on campus • Study has provisions to waive consent in emergency circumstances • Involves enrollment of vulnerable population(s)

*Require an independent Medical Monitor or Safety Monitoring Committee as determined by CTSRMC and DSMC.

NOTE: The amount of oversight provided by an external sponsor does not modify or eliminate the need for investigators to oversee, in an ongoing manner, the conduct of his/her research and follow the MP submitted to the CTSRMC.

CLINICAL TRIALS SCIENTIFIC REVIEW AND MONITORING COMMITTEE (CTSRMC)

Overview of CTSRMC

The Abramson Cancer Center (ACC) established a comprehensive Protocol Review and Monitoring System (PRMS) in 1992 known as the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC). The Committee's focus is scientific merit, priorities, and progress of cancer relevant protocols conducted within the University of Pennsylvania and Children's Hospital of Philadelphia (CHOP). Presented below is an overview of the PRMS as administered by the CTSRMC.

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 full University IRB approval. The Perelman School of Medicine (PSOM) is committed to supporting the mission of the ACC CTSRMC, and has worked collaboratively with the ACC to achieve the mission outlined by NCI in the CCSG. Because the ACC recognizes the critical role human subjects research plays in providing treatment options to subjects and expanding our knowledge of this life-threatening disease, the CTSRMC Chairs and Director report directly to the Cancer Center Director to ensure the needs of the core Grant are met, however, in order to maintain the integrity and autonomy of this Committee, the Cancer Center Director does play a role in the scientific review process and does not influence any of the Committee's decisions.

Consistent with NCI Core Grant guidelines, the CTSRMC reviews the scientific merit, statistical design, feasibility, competitiveness, ongoing accrual performance and scientific progress of cancer-related protocols. However, different levels of review exist based on the sponsor type, funding source, study populations and study design.

For multi-site institutional trials at cancer centers with an NCI approved PRMS (scientific review committee), the PRMS of the lead site is responsible for the full scientific review of the protocol. The other participating sites are responsible only for an expedited review focused on prioritization, competing studies, and feasibility at that site. Should the PRMS at the lead site be conditionally acceptable or unacceptable, participating sites may select a single, acceptable PRMS at a participating NCI-designated cancer center to conduct the full scientific review.

- **Study teams are required to provide the CTSRMC with documentation of protocol review and approval by another PRMS at the time of submission.**
- **Study teams are required to provide proof that the PRMS at the other cancer center is fully NCI approved.**

Per the institutional agreement with the NCI, the Penn and CHOP IRBs will not grant full approval to any cancer-based protocol without receiving documentation of full CTSRMC/PPRC approval. Additionally, the CTSRMC/PPRC has the authority to open protocols that meet the scientific merit and scientific priorities of the center and to terminate protocols that do not demonstrate adequate scientific progress.

Pediatric protocols are reviewed by an expert Sub-committee of the CTSRMC. The Pediatric Protocol Review and Monitoring Committee (PPRC) is based at Children's Hospital of Philadelphia (CHOP). The PPRC follows the same policies and procedures as the CTSRMC and is overseen by the CTSRMC Chairs and Director.

CTSRMC and PPRC Members

The CTSRMC and PPRC comprise 48 qualified, committed faculty members from a broad range of clinical research disciplines who have expertise in conducting human subjects research. The CTSRMC/PPRC is required by the ACC to have broad representation from cancer-related specialties, such as medical, radiation, and surgical oncology, head and neck cancer, pulmonary medicine, internal medicine, psychiatry, pediatric oncology, and gynecological and neurological oncology, as well as laboratory and population sciences, pathology medicine, pharmacy and biostatistics. Committee members are carefully selected based on their research interests and expertise in the design and conduct of clinical research, as well as their personal commitment to the scientific review process.

Study Sources:

Study source is an NCI term that allows the ACC to identify the sponsor type, and is used by the CTSRMC and DSMC for review categorization and for study data transmission to the NCI Clinical Trials Reporting System (CTRP).

Funding Source:

The specific name of the sponsor. This categorization further clarifies the Study Source and is included in the study data transmission to the NCI Clinical Trials Reporting System (CTRP).

Study Source: National

NCI National Clinical Trials Network (NCTN) and other NIH-supported National Trial Networks

NCI-NCTNAlliance for Clinical Trials in Oncology

- American College of Surgeons Oncology Group
- Cancer and Leukemia Group B

North Central Cancer Treatment GroupChildren's Oncology GroupECOG-ACRIN Cancer Research Group

- American College of Radiology Imaging Network
- Eastern Cooperative Oncology Group

NCIC Clinical Trials Group (Canadian Cancer Society)NRG Oncology Group

- National Surgical Adjuvant Breast & Bowel Project
- Radiation Therapy Oncology Group
- Gynecologic Oncology Group

SWOG**NIH National Trial Networks:**

There are many networks under every NIH institute. Networks are identified by conducting a web-search under the respective Institute. Networks not found under an Institute will not be categorized as an NIH network unless the PI can provide qualifying documentation.

Study Source: Externally Peer-Reviewed

R01s, SP0RES, U01s, U10s, P01s, CTEP, or any other clinical research study mechanism supported by the NIH or organizations. The NIH and all of the funding organizations listed below employ: 1) a peer review system that uses primarily external reviewers and is free of conflict-of-interest; (2) a ranking or rating system in the review process based on the scientific merit of the proposed research; and (3) a funding system based primarily on the peer review ranking or rating of the research applications. All funded, multi-year research projects from these organizations (excluding pilot projects and feasibility studies) may be counted toward the requirements noted above. In addition, these projects may receive support from CCSG shared resources.

1. Agency for Healthcare Research and Quality (AHRQ)
2. Alex's Lemonade Stand Foundation (ALSF)
3. American Association of Cancer Research (AACR)
4. American Cancer Society (ACS), (national office only)
5. American Foundation for AIDS Research (amfAR)
6. American Institute for Cancer Research (AICR)
7. California Institute for Regenerative Medicine (CIRM)
8. Cancer Prevention Research Institute of Texas (CPRIT)
9. Center for Disease Control and Prevention (CDC)
10. Central Office of the Veterans Administration (VA), (excluding local/regional and "block" grants)
11. Environmental Protection Agency (EPA)
12. The Flight Attendant Medical Research Institute (FAMRI)
13. Florida Biomedical Research Program (FBRP)
14. Food and Drug Administration (FDA)
15. Howard Hughes Medical Institute (HHMI)

16. Leukemia and Lymphoma Society (LLS)
17. Melanoma Research Alliance (MRA)
18. Multiple Myeloma Research Foundation (MMRF)
19. National Institute for Occupational Safety and Health (NIOSH)
20. National Science Foundation (NSF)
21. New York State Department of Health Wadsworth Center/New York State Stem Cell Science Program (NYSTEM)
22. Patient-Centered Outcomes Research Institute (PCORI)
23. Prevent Cancer Foundation (PCF)
24. Prostate Cancer Foundation (PCF)
25. Susan G. Komen for the Cure
26. The California Breast Cancer Research Program (CBCRP)
27. The California Tobacco Related Disease Research Program (TRDRP)
28. U.S. Army (DOD) special research programs *

***Note:** Grants funded through the U.S. Army's, (DOD) special research programs in ovarian, breast and prostate cancer may also be listed in the category of peer reviewed funded grants

Study Source: Institutional

In-house clinical research studies authored or co-authored by Cancer Center investigators and undergoing scientific peer review solely by the CTSRMC. The Cancer Center investigator has primary responsibility for conceptualizing, designing, and implementing the clinical research study and reporting results.

- It is acceptable for industry and other entities to provide support (e.g., drug, device, other funding), but the trial should clearly be the intellectual product of the center investigator

This category may also include:

- Institutional studies authored and implemented by investigators at another Center in which the ACC is participating **if** the ACC investigator is not receiving support from the other center or if the ACC investigator is helping to steer the ongoing progress of the study.
- Multi-Institutional studies authored and implemented by ACC investigators.
- Studies that meet the above definitions but are funded via NCTN or External Peer Review are categorized by the funding mechanism with an indicator that they are investigator-initiated. These studies are not considered institutional.

Study Source: Industrial

A pharmaceutical/biotech company controls the design and implementation of these clinical research studies. The protocol is the full intellectual property of the company, and the company has full legal and regulatory responsibility for the study.

Clinical Research Categories

These categories are used by the CTSRMC and DSMC and are included in the study data transmission to the NCI Clinical Trials Reporting System (CTRP)

- **Interventional (INT):** Clinical Research Category in which individuals are assigned by an investigator based on a protocol to receive specific interventions. The participants may receive diagnostic, therapeutic, behavioral or other types of interventions. The assignment of the intervention may or may not be random. The participants are followed and biomedical and/or health outcomes are assessed.
- **Observational (OBS):** Clinical Research Category in which the studies focus on cancer patients and healthy populations that involve no intervention or alteration in the status of the participants. Biomedical and/or health outcome(s) are assessed in pre-defined groups of participants. The participants in the study may receive diagnostic, therapeutic, or other interventions but the investigator of the observational study is not responsible for assigning specific interventions to the participants of the study.
- **Ancillary or Correlative (ANC/ COR):**
 - Ancillary: studies 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. Ancillary studies must be linked to an active clinical research study and should include only patients accrued to that clinical research study. Only studies that can be linked to individual patient or participant data should be reported.

- Correlative: 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.

Primary Purpose of Reviewed Protocols

These categories are used by the CTSRMC and DSMC and are included in the study data transmission to the NCI Clinical Trials Reporting System (CTRP)

- **Basic Science (BAS):** Protocol designed to examine the basic mechanisms of action (e.g., physiology, biomechanics) of an intervention.
- **Device Feasibility (DEV):** Protocol designed to evaluate one or more interventions for the feasibility of the product or to test a prototype device and not health outcomes. Such studies are conducted to confirm the design and operating specifications of a device before beginning a full clinical trial.
- **Diagnostic (DIA):** Protocol designed to evaluate one of more interventions aimed at identifying a disease or health condition.
- **Health Services Research (HSR):** Protocol designed to evaluate the delivery, processes, management, organization, or financing of health care.
- **Prevention (PRE):** Protocol designed to assess one or more interventions aimed at preventing the development of a specific disease or health condition.
- **Screening (SCR):** Protocol designed to assess or examine methods of identifying a condition (or risk factor for a condition) in people who are not yet known to have the condition (or risk factor).
- **Supportive Care (SUP):** Protocol designed to evaluate one or more interventions where the primary intent is to maximize comfort, minimize side effects, or mitigate against a decline in the participant's health or function. In general, supportive care interventions are not intended to cure a disease.
- **Treatment (TRE):** Protocol designed to evaluate one or more interventions for treating a disease, syndrome, or condition. Note: This equates to therapeutic trials in previous versions of the guidelines.
- **Other (OTH):** Not in other categories

Submission of Protocols to the CTSRMC

All cancer-related protocols require some level of CTSRMC review (exemption, expedited or full-board). A complete protocol packet includes (as applicable): the current protocol, current study and HIPAA consents, Study Monitoring Plan, Justification and Prioritization form, CRF's (in-house), Investigator's Brochure (where applicable) and documentation of IND/IDE exemptions/acknowledgement. **Grant applications are not considered protocols and are not accepted by the Committee for protocols that require full-committee review.** Investigators must electronically submit a complete protocol packet to the CTSRMC via the Human Subjects Electronic Research Administration (HSERA) portal. This portal is a central repository for protocols that may be accessed by all institutional review entities. This single site of submission significantly decreases the regulatory submission timeframe, allows multiple review bodies to harmonize and streamline their reviews and importantly ensures version control of key protocol documents. All of these efficiencies positively affect the time-to-activation.

Submission of Protocols to the PPRC

The PPRC reviews protocols using the same review category criteria and processes as the CTSRMC (parent committee). 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 via e-mail to the PPRC Coordinator two weeks prior to the meeting. The PPRC and CHOP institutional review entities do not yet have a common portal for submission.

Scientific Review of Protocols

The CTSRMC and PPRC review protocols by Exemption, Expedited and Full-Committee. Each review type is intended to allow the ACC to track all cancer-related research being conducting at Penn while decreasing unnecessary barriers to activation.

Exempted from Review protocols

Per the NCI guidelines, the CTSRMC is not required to evaluate or prioritize studies dealing with healthy human subjects and the population sciences, e.g., observational and epidemiologic studies. Protocols that fall under these categories receive CTSRMC administrative acknowledgement (documented exemption) regardless of the sponsor type/funding source. To ensure that the ACC is aware of all cancer-relevant

research at Penn, the CTSRMC requires registration of these protocols, but no longer conducts any level of scientific-peer review for merit, relevancy, feasibility, competitiveness or prioritization. Such studies are granted an administrative acknowledgement that documents exemption from CTSRMC full-board and expedited review. Investigators are not required to submit amendments or annual continuing review documents. These studies are not monitored for accrual performance or scientific progress. These studies must continue to register all enrolled subjects in the ACC CTMS. In addition, protocols dealing with biobanks, development of databases and retrospective chart reviews and anonymized surveys/questionnaires also qualify for CTSRMC exemption. Administrative acknowledgement is usually issued within three business days of submission.

For purposes of CTSRMC exemption review:

- **Healthy Patients** are those who have no morbidities, or any morbidity that is not cancer or pre-cancer.
- **Population Sciences** are:
 - Research examines effects of interventions to slow or halt risk factor or disease development or progression; interventions use high-risk individual and population approaches, including medications (to modify behavior), non-medication behavioral strategies, and environmental change. Studies examine lifestyle, nutrition and exercise, psychological and sociocultural factors, and environmental and genetic influences relevant to prevention.
 - **NOTE: Use of medication on these studies is not intended for the treatment of cancer, cancer treatment-related conditions (e.g., GVHD, cardiac issues, CRS, TLS, pain management, mucositis, etc.) or pre-cancer (a condition that may [or is likely to] become cancer, pre-malignant lesions where there is a clear evidence of association with increased risk of invasive cancer, chronological evolution of the lesions result in progression to invasive cancer or regression, lesions differ from normal cells and share molecular and phenotypic features with invasive cancer, invasive cancer originates from the pre-malignant lesion.)**
 - Clinical application research examines approaches to improve healthcare delivery and patient outcomes. Studies include clinical and community trials and observational studies.
 - Studies are conducted to identify temporal trends and population patterns in the prevalence, incidence, morbidity, and mortality and include single- and multi-center observational epidemiology studies of the development, progression, and treatment.
 - Studies also identify environmental, lifestyle, physiological, and genetic risk factors for disease and risk factor development, including characterization of gene/gene and gene/environment interactions.

Expedited Review protocols

- Studies sponsored by NCI-sponsored NCTN, NIH National Trial Networks, and those that have received External Peer-Review (EPR) supported by the various NIH mechanisms (e.g., ROIs, U01s, U10s, P01s, and P50s, etc. https://grants.nih.gov/grants/funding/ac_search_results.htm, other approved funding agencies as detailed below (Organizations with Peer Review Funding Systems) and clinical research protocols approved by the NCI's Cancer Therapy Evaluation Program or the Cancer Control Protocol Review Committee are reviewed via an expedited review. Although these protocols are excluded from full-committee scientific peer review, they are evaluated for local feasibility and prioritization via an expedited review mechanism, and are reviewed for accrual and scientific progress once opened. Per guidance from NCI staff, the CTSRMC reserves the right to issue stipulations if serious safety concerns are identified. The expedited review mechanism does not duplicate the external peer review process which includes protocol design and statistics.
- Compassionate Use and Expanded Access protocols are also reviewed via an expedited mechanism since these protocols are not designed to answer formal scientific questions.
- Correlative or laboratory-based studies are reviewed via an expedited mechanism. Correlative studies that are linked to a protocol that requires full-committee review, may, at the discretion of the Committee Chairs, be routed to full-committee review if the Chairs believe the protocol to which the correlative study is linked cannot be fully understood by members without knowledge of the correlative study.

Protocols appropriate for expedited review may be submitted at any time and are reviewed by a Chair, Biostatistician (if applicable), and CTSRMC Director (if applicable). At the discretion of the reviewing Chair, additional review for specific expertise may be sought from Committee members. The average time from submission to review is three business days and a response from the CTSRMC/PPRC is usually received within five business days of the submission.

Full-committee protocols

There are several steps researchers are encouraged to take prior to submitting a protocol for full-board review. These include: scheduling a meeting with a member of the Biostatistics Core to ensure that the protocol has a sound statistical plan; consultation with one of the ACC's centralized Clinical Research Units to review the protocol's project and data management needs; consultation with CPDM staff to review the protocol's project and data management needs; discussion with the DSMC to develop an appropriate monitoring plan; review of the protocol with CTSRMC staff to make certain the protocol is complete and to coordinate the two-step review process if desired.

All cancer treatment and other selected intervention studies, not included in the review categories above, require full-committee review. CTSRMC meetings are held on the second and fourth Mondays of every month. Additional details about CTSRMC meetings, requirements, processes and deadlines can be found on the CTSRMC website www.ctsrcmc.org.

For **Committee Meeting #1**, protocols must be submitted no later than noon on the last business day of the month preceding the meeting.

For **Committee Meeting #2**, protocols must be submitted no later than noon on the 15th of the month. If the 15th is on a Saturday or Sunday, the deadline is noon on the Friday before the 15th.

Full-committee protocols are assigned to a primary reviewer with expertise in the targeted disease or modality, a secondary reviewer who is one of the Chairs and a biostatistical reviewer is assigned based on his/her statistical expertise. The CTSRMC Director, reviews all protocols for quality, inclusion of women/minorities and regulatory issues. Protocol review is not limited to those reviewers assigned to the protocol. Feedback from all members is sought and encouraged. The average time from submission to review is six business days and a response from the CTSRMC/PPRC is usually received within three business days of the full convened meetings.

The CTSRMC has developed a Scientific Review guidance document using NIH standards 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 (*visit our website www.ctsrcmc.org for details*).

Committee Review of Process

When a protocol is scheduled for review, the PI is sent a notice of review and is encouraged (although not required) to attend the review of his/her protocol. No less than five 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 Coordinators to be read by the Chair during the meeting.

During the Committee meeting, the primary, secondary, biostatistical, and regulatory reviewer (if applicable) discuss the study in detail, including the study design, appropriateness for the institution and patient populations, feasibility of conducting the protocol, statistics, adequacy 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 documented on the reviewer's form, included in the CTSRMC minutes, and are subsequently included in the letters sent to PIs. Most members also provide verbal comments based on their area of expertise during meetings whether or not formally 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. Studies that have been approved are assigned a risk level which dictates the required level and frequency of DOCM auditing. Protocols that were disapproved require a full re-review by the original reviewing committee in order to gain approval. Should a committee member be unable to attend a meeting, his/her written review can be submitted via e-mail to the CTSRMC/PPRC office to be read by the Chair during the meeting. Conflicted members must recuse themselves from discussion about the protocol and may not vote on approval.

Satisfactory resolution of all deficiencies identified by the Committee must occur before a protocol may receive 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. All documentation is loaded into HSERA so that the University's IRB can determine when it is appropriate to issue a final full IRB approval.

Following review of a protocol by the PPRC, the protocol must undergo an administrative review and receive approval from a CTSRMC Chair prior to the PPRC granting final approval. The CTSRMC may request additional clarification/information as deemed necessary in order to accept the PPRC review outcome.

Protocol Review Criteria

Each reviewer must complete an electronic review document that is turned in to the Chair and CTSRMC Director at the conclusion of the meeting. The review criteria that are used to assess scientific rationale, study design, expected accrual rates, biostatistical input and feasibility for completion within a reasonable time period are detailed below. (*visit our website www.ctsrc.org for details*)

Significance

- Does this study address an important problem?
- If the aims of the protocol are achieved, how will scientific knowledge or clinical practice be advanced?
- What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Approach

- Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project?
- Does the protocol acknowledge potential problem areas and consider alternative strategies?

Innovation

- Is the protocol original and innovative?
- Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

Feasibility

- For this study is it feasible to relate endpoints to objectives?
- Is the study designed in such a way that it can be conducted at this institution?

Competing studies

- Are there other studies currently open or in development that will directly compete with this study for subjects?
- If there are competing studies, is there a plan for managing how subjects will be routed to each study?
- Are there currently studies open that are better options for subjects than this study?
- If there are competing studies that are better options for subjects, is it likely that this study will meet its accrual goal?

Women, Minorities and Children

- The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed.

Statistical Design

- Correct statistical model being used
- Accrual rate and/or study duration
- Sample size justified
- Maximum number of patients justified
- Appropriate outcome parameters
- Stopping guidelines
- Clear specification of primary and secondary hypotheses
- Adequate proposed testing of primary and secondary hypotheses
- Primary endpoints for interim and final analysis
- Plans for data analysis
- Clear statement of data analysis in relation to objectives
- Method of randomization and stratification (as applicable)
- Error levels (alpha and beta) (as applicable)
- Differences to be detected for comparative studies (as applicable)
- Size of the confidence intervals to be constructed around the estimated outcomes (as applicable)
- Hypotheses to be tested in ancillary studies (as applicable)

At the conclusion of the review the Committee votes on whether or not the protocol will be approved, approved with stipulations or disapproved. All protocols that fall into one of the approved categories are assigned a priority score as follows:

- 1.0-1.9 (outstanding science, high priority, important)
- 2.0-2.9 (good science, lower priority, worthwhile,)
- 3.0-3.9 (no scientific impact, no priority, not worthwhile)

This score should be used by ACC research programs to prioritize their research portfolios and resource allocation thus ensuring that the most important and impactful research is appropriately supported.

Two-Stage CTSRMC/PPRC Review

Early in the development of their protocols, investigators may request a two-stage CTSRMC/PPRC review. The availability of this review process option improves the quality of protocols submitted to both the CTSRMC/PPRC and IRB, streamlines the process of gaining final approval and reduces staff development efforts. It is especially valuable for junior investigators. In this process the Committee reviews the protocol in the standard manner but will not make a formal determination of approval or assign a priority score. **Note:** Protocols submitted for the double-review process must have been vetted for acceptance and prioritization by the disease-specific team and/or cancer center program prior to being submitted so as to not place unnecessary administrative burdens on support staff and the Committee.

CTSRMC Review and Access to ACC Core Resources

All protocols approved by the CTSRMC for merit, regardless of review type, have access to CCSG-supported centralized resources such as informatics, biostatistics, and clinical protocol and data management.

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 cancer-treatment studies at entities not considered Abramson Cancer Center with the goal of ensuring high quality research. Investigators must submit the justification form (*visit our website www.ctsrcmc.org for details*) with the study protocol. The CTSRMC reviews the justification request and determines whether or not the 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, because investigators are fully responsible for the oversight of every external site, which is a complicated responsibility, the CTSRMC may, at its discretion, set restrictions on the number of sites to be opened 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.

ACC Defined Essential Monitoring Plan Elements

In general, a MP (*visit our website www.ctsrmc.org for details*) 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 Plans are considered a formal part of study approval, and investigators are expected to adhere to the MP, without deviation, for the duration of the study. Failure to follow the MP violates the terms of CTSRMC approval and may be grounds for study closure.

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), GMP (Good Manufacturing Practice) and GLP (Good Laboratory Practice). Examples of these types of clinical trials include vaccines; adoptive therapies, gene transfers, imaging agents, etc. Trials such require a Medical Monitor, Safety Monitoring Committee or Data and Safety Monitoring Board (depending on the study phase and design) as well as personnel with expertise in GLP and GMP. The PI must develop a custom comprehensive monitoring plan under the guidance of the DOCM before the study can receive full CTSRMC approval. (*visit our website www.ctsrmc.org for details*).

Procedure for Submission of a Monitoring Plan to the CTSRMC

All protocols submitted to the CTSRMC must use an ACC DOCM developed Monitoring Plan template. Following receipt of the protocol, the CTSRMC Coordinator conducts an initial administrative review to ensure that the correct MP template has been submitted, that it is complete and signed and dated by the PI within 30 days of the submission. The protocol will be returned to the investigator as incomplete if there are any MP issues. 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. 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 (*visit our website www.ctsrmc.org for details*) of this document.

Process and Criteria for Prioritizing Protocols

The process for prioritizing clinical protocols lies initially with the disease-specific teams and cancer center core grant programs. The CTSRMC/PPRC expects that all protocols that are submitted have been reviewed by the disease programs leaders for appropriateness and prioritization within the program's portfolio prior to being submitted for review. Additionally, the CTSRMC/PPRC administrative office generates a monthly report on all potentially competing protocols currently open campus-wide. This report is provided to the Chair at the beginning of each meeting. 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. This plan must include a statement of support from the disease-specific team leader or the program leader. Protocols will not receive full approval until the Chair is satisfied with the proposed plan. Also, although externally peer reviewed and funded protocols are not reviewed for scientific merit, they are administratively reviewed for prioritization and competitiveness with other ongoing or proposed studies at our Center. Finally, the CTSRMC/PPRC assigned priority score is provided to each disease-specific team and cancer center program and this score is to be used to prioritize projects within the team/program.

Justification and Prioritization form

The J&P form (*visit our website www.ctsrmc.org for details*) is where the PI formally documents the initial prioritization by the disease team and/or ACC program team, provides details about their current research portfolio prioritization and prioritization within the disease team among other key points that facilitate CTSRMC review. The Justification and Prioritization (J&P) form must be submitted with all full-committee protocols. It must be completed by the PI and signed and dated within 30 days of protocol submission.

Protocols submitted with the J&P form issues will be returned to the PI as incomplete. A J&P form is not required for expedited or exempt protocols.

Relationship of CTSRMC/PPRC and IRB

The CTSRMC and PPRC are separate and independent of the institutional IRBs. The roles of the CTSRMC/PPRC are complementary to, and do not duplicate or overlap any of the responsibilities of the IRBs. The primary focus of the CTSRMC/PPRC 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, equipoise and informed consent procedures. The University of Pennsylvania IRB and CHOP's IRB will not grant final approval for any cancer-related protocol or allow a protocol to open for enrollment until final approval is granted from the CTSRMC/PPRC. This agreement has been in place at the University of Pennsylvania since 1992 and Children's Hospital since 2001.

Time to Activation

The CTSRMC/PPRC administrative offices carefully track all protocol transactions to and from the Committees and the IRB. These data allow the Committees to closely monitor their own performance as well as the performance of investigators in regards to response times and the quality of responses. Data points such as the date the protocol was submitted, the date it was assigned to for review, the date it was reviewed, the date the stipulation letter was written, the date the stipulation letter was sent to the PI, the date the PI responded, etc. are tracked. Tracking continues for the lifecycle of the protocol and does not end with study activation. The time from Committee approval to the time of study activation depends on a number of factors such as the speed with which the PI responds to stipulations, completeness of the PI's responses to stipulations, final approval from the IRB and other required review bodies (i.e. Radiation Safety, Biosafety, etc.) as well as resolving other administrative and operational items. In regards to the time-to-activation, the Committees generally send initial review letters within two to three business days of the monthly meetings and respond to addressed stipulations within three to four business days of receipt.

Monitoring Protocols for Progress and Performance

In addition to the initial review of protocols for approval, the CTSRMC/PPRC conducts ongoing review of protocol progress and performance for applicable protocols through close accrual monitoring and review of the annual Continuing Review documentation. The CTSRMC/PPRC has the authority to close or terminate a protocol for poor accrual and/or scientific progress. Studies with unique accrual targets such as those considered to be rare cancers and targeted therapies focusing on types and sub-types are excluded from accrual and scientific performance monitoring.

- Accrual Monitoring- Evaluated for accrual progress three months from the date approved by the CTSRMC and every three months thereafter. 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. The CTSRMC/PPRC 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 to twelve month extension at his/her discretion. 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. If the study is allowed to remain open, but has not improved enrollment by the next review window anniversary, the CTSRMC/PPRC Chair will notify the PI that the Committee has closed/terminated the study. When a study is closed by the CTSRMC/PPRC, the IRB is notified of the change in study status.
- Scientific Progress Monitoring- Every protocol approved via full-committee (with the exception of unique accrual targets) is reviewed at least annually to assess whether or not the study is making appropriate scientific progress. The Chair and CTSRMC Director review the annual IRB Continuing Review, publications and additional documentation as applicable, for example, IND updates to FDA and DSMB reports. If the Committee believes the study is not making sufficient progress, the research question or therapy is no longer relevant, or the study is no longer meritorious, the CTSRMC/PPRC will close/terminate the study.

Additional Monitoring Required by the CTSRMC

- **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. (*visit our website www.ctsrc.org for details*)

- **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 Charter, frequency of DSMB meetings and a proposed list of data items to be provided to the DSMB should be provided to the CTSRMC. 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). (*visit our website www.ctsrc.org for details*) 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.

Conflict of Interest

The CTSRMC approaches Conflict of Interest from two perspectives. Conflict of interest related to review of protocols and confirmation that protocols with conflicts have documentation from the University's Conflict of Interest Standing Committee that a COI plan has been put into place.

- Committee Members COI

Protocols are assigned to reviewers by CTSRMC Coordinators and approved by the CTSRMC Director who reviews every protocol to ensure members are not assigned a protocol on which they will be involved. Members are reminded that they must announce any COI and recuse themselves from review and/or discussion of any protocol on which they serve as PI, sub-investigator, Medical Monitor, Statistician or any other supporting role consultative role. Members that recuse themselves are not allowed to vote on approval.

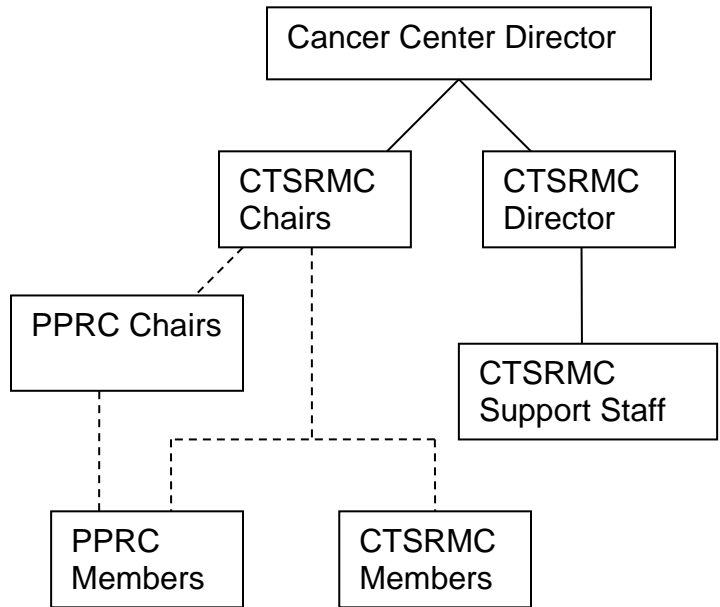
- Conflict of Interest Standing Committee

The University of Pennsylvania has a Conflict of Interest Standing Committee (COISC) that is charged with evaluation and assessment of potential conflicts and the COISC develops the management plan to address the areas vulnerable to conflict such as (safety, outcome, data integrity etc.) to which the PI and study team must adhere. The CTSRMC will not grant final approval to a protocol until COISC approves the COI management plan, and all necessary amendments to the study documents have been made. In the event, the CTSRMC believes there is a COI that was not revealed to the COISC, the CTSRMC will identify the potential conflict and require the PI to submit to the COISC for evaluation.

Ongoing CTSRMC approval

All protocols (see review section for exclusions) that have received CTSRMC approval via either expedited or full-committee review must send all amendments to any study documents to the CTSRMC/PPRC for review and approval before or at the same time that they are sent to the IRB. Documents should be sent via the common listserve CTSRMC_Submissions@lists.upenn.edu. These requirements (and others) are outlined in the initial CTSRMC approval letters. Failure to comply with all approval criteria may result in study holds or closures.

CTSRMC STRUCTURE



DATA AND SAFETY MONITORING COMMITTEE (DSMC)

Overview of the DSMC

In response to the NCI requirement for Cancer Centers to develop Data and Safety Monitoring programs, the ACC established in 2001 a comprehensive Quality Control (QC), Quality Assurance (QA), Regulatory Affairs (RA) and Pharmacovigilance (PV) system for all cancer-related human subject research. These responsibilities are partially met through the Data and Safety Monitoring Committee (DSMC), which oversees study monitoring and auditing, safety reviews, and the development of study Monitoring Plans (MP), as well as adherence to the Cancer Center's NCI approved institutional Data and Safety Monitoring Plan. The DSMC Chair, Vice Chair and Director report directly to the Cancer Center Director to ensure the needs of the core Grant are met, however, in order to maintain the integrity and autonomy of this Committee, the Cancer Center Director does not play a role in the quality control and assurance process and does not influence any of the Committee's decisions. 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 DSMC sub-committee. CRQA meets the second Friday of every month.

Members of DSMC

The DSMC is a multi-disciplinary committee that consists of a core group providing the necessary expertise in clinical oncology and human subject research with additional representatives from biostatistics. The DSMC has ten oncology clinical investigators spanning medical, surgical and radiation oncology along with key disease site expertise; a biostatistician; the Director of the DSMC, who serves as the Cancer Center's regulatory affairs specialist; and the DSMC Manager of Regulatory Compliance. The DSMC also has ad hoc consultant members representing other cancer disease sites and modalities if needed for additional expertise.

Members of CRQA Committee

CRQA has eight oncology clinical investigators; biostatistics; late effects; and the Director of the DSMC. CRQA also has consultant members representing each pediatric cancer disease site and modality.

Responsibilities of the DSMC/CRQA

The DSMC/CRQA accomplishes its goals by reviewing subject safety issues and reports, evaluating protocol exceptions and deviations, assessing and/or developing study Monitoring Plans, examination of reviews conducted by Medical Monitors, Safety Monitoring Committees and Data and Safety Monitoring Boards (DSMB) for in-house and ACC investigator-initiated EPR studies. In addition, the DSMC establishes the expectations for frequency and depth of study audits which are conducted on its behalf by the DOCM, reviews audit outcomes, and works with the DOCM Director to define Corrective Action Plans (CAP) that are required as a result of audit.

Documentation of monthly compliance activities, mandated corrective actions; a comprehensive table of adverse event reports generated from the PV database and other study, center, institutional or federal issues related to quality and safety are reviewed by members at each meeting.

The Committee may, at its discretion, mandate an investigator implement a Corrective Action Plan (CAP) based on issues reviewed during the monthly meeting. In the event the issue impacts subject safety, the IRB is notified of Committee actions. The committee may also request follow-up information on recorded and/or reported AEs/SAEs; make recommendations in regards to the status of the study or consent form modifications if there are concerns about safety or quality; request additional documentation from the study Medical Monitor, Safety Monitoring Committee or Data and Safety Monitoring Board; and request information from the sponsor as deemed necessary by the Committee. The DSMC/PPRC has the authority to suspend or terminate a protocol, investigator or program for safety concerns and/or major audit deficiencies. In the event

of a DSMC/PPRC mandated suspension or termination, the IRB is immediately notified of the action and will concur, and thus, all activities will cease until issues are resolved to the satisfaction of the DSMC/CRQA. For federally-funded studies that require DSMC/PPRC mandated suspension or termination, the DSMC Director will notify the NCI program director responsible for the grant.

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 (or designee) 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 compliance activities. Ongoing references to DSMC activities should be understood to include CRQA activities as well.

Relationship of the DSMC and CTSRMC

The DSMC functions independent of the CTSRMC but communicates issues related to scientific progress, safety or integrity to the CTSRMC as necessary. Additionally, the CTSRMC assigns the initial study risk (defined by the DSMC) at the time of scientific review which sets the stage for the compliance activities and oversight conducted by the DSMC. These committees function independently without overlap.

Monitoring Plans

• In-House and 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 auditing 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 DOCM that provides for complete quality assurance of the study. If the study is CTEP funded, the investigator must also use the reporting requirements and schedules used by CTEP for handling Adverse Events, Adverse Drug Reactions (ADR) and Serious Adverse Events (SAE) (*visit our website www.ctsrc.org for details*). This plan is required with all new CTSRMC Full-Committee submissions.

• Multi-Institution Investigator-Initiated Studies

While the ACC recognized the need to make certain studies available to other non ACC 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. In addition to completing the **in-house monitoring plan template**, the PI must develop a comprehensive study specific **Multi-Site Manual of Procedures** (*visit our website www.ctsrc.org for details*) 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 PennCTMS (Velos eResearch)
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. Each manual is customized for the specific study and is developed with consultation from the DOCM. The manual describes in a step-wise manner all of the responsibilities of the coordination site, the research sites, how data flows between sites to the Data Coordinating Center (DCC), shipment of drugs/agents, monitoring and auditing, data sharing, management of events etc. Flow diagrams are included to detail operational management of the DCC and participating sites.

DOCM auditors will only audit the main ACC site. All other sites must be monitored by the study PI or a contracted monitoring agency.

- **NCI Cooperative Group Studies**

Each national group conducts a range of therapeutic and non-therapeutic studies. Because each group through NCI 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 PI trial oversight that compliments that of the cooperative group. The Cancer Center's DOCM has developed a template that fulfills this requirement.

- **Industry Studies**

All clinical trials conceived, initiated and regulatory sponsored by pharmaceutical or biotechnology sponsors with subsequent Cancer Center participation required the PI to complete a sponsored monitoring plan template that will provide for PI 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 DOCM 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. If the study has no external monitoring or auditing, the study will be audited by DOCM auditors based on its risk assignment.

Study Exceptions and Deviations

The DSMC's definitions and process for review of protocol deviations and exception is harmonized with Penn's IRB. The DSMC's review is in addition to, but compliments and supports the IRB's review.

Exceptions

A prospective, one time, intentional action or process that departs from the CTSRMC and IRB approved study protocol, intended for **one** occurrence. PIs cannot ask for approval to apply the same exception across potential future subjects. In that event, the study protocol must be amended. **Only protocols that were reviewed by the CTSRMC via full-committee are required to request exceptions form the DSMC.**

Exception requests must be submitted to the DSMC via the compliance listserv
DOCM_Compliance@lists.upenn.edu

- For in-house or studies: Exception requests must include the rationale, sufficient details about the subject to help the DSMC understand the clinical and scientific impact of the request, the impact on the protocol endpoints, the specific timeframe in which the exception is needed and whether or not the exception will include a protocol amendment. The DSMC will review the exception and may request additional information at its discretion.
 - For in-house and investigator-initiated 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.
- For externally sponsored protocols: Documented notification of the sponsor with the sponsor's response must be submitted with your exception request to the DSMC. The DSMC acknowledges and does not comment on exceptions that are approved or acknowledged by sponsors. Some sponsors will not approve or acknowledge an exception request and will advise the PI that if they decide to move forward,

that they will have a documented deviation. In this case, the DSMC will offer an opinion, but will not prevent the PI from moving.

Upon receipt of an exception request, the DSMC (at least a Chair and two other members) will review the request within 24 hours (or in an urgent manner as applicable) and the PI will be notified of the Committee's decision. The DSMC may request additional information to assist with the determination. The IRB will be copied on the final DSMC decision. The DSMC may also request that the DOCM conduct follow-up compliance activities to address issues revealed by the exception request.

Deviations

An accidental or unintentional change to the CTSRMC and IRB approved protocol that placed one or more participants at increased risk, has the potential to occur again, or has the potential to qualify as serious or continuing noncompliance. Such deviations must be reported to the DSMC within five business days and the IRB within ten business days of when the event became known to any member of the study team. **Only protocols that were reviewed by the CTSRMC via full-committee are required to report deviations to the DSMC.** Deviation reports must be submitted to the DSMC via the compliance listserve DOCM_Compliance@lists.upenn.edu

- For in-house or studies: Deviations must include the IRB a full description of the deviation, date it occurred, data is was identified, if there were delays in identify the deviation, and explanation for the delay, the PIs assessment of the impact of the deviations, corrective action plan to fix the issue and to prevent such issues for occurring in the future, and a statement about whether or not a protocol amendment will be needed as part of the CAP. The DSMC will review the deviation and may request additional information at its discretion.
 - For in-house and investigator-initiated studies with a Medical Monitor or Safety Monitoring Committee (not DSMB): Documentation that the monitoring body was notified of the reportable event must be included with your submission.
- For externally sponsored protocols: Documented notification of the sponsor with the sponsor's response must be submitted with your report. The DSMC acknowledges or may comment on exceptions that were identified or addressed by corrective actions with the guidance of the sponsor.

Other non-reportable deviations should be documented in a memo to file or on a deviation log Documentation must include the PI's assessment of the impact of the deviation on subject safety and/or study endpoint and outcome integrity and must be signed by the PI. Deviations that do not include the PIs documented assessment are not acceptable. (*visit our website www.ctsrmc.org for details*)

Upon receipt of a deviation request, the DSMC (or at least a Chair and one member) will assess the the deviation. The PI will be notified of the Committee's assessment. The DSMC may request additional information to assist with the assessment. The IRB will be copied on the final DSMC decision if the Committee believes the deviation affected subject safety or study integrity. The DSMC may also request that the DOCM conduct follow-up compliance activities to address issues revealed by the deviation report.

Auditing Timelines

The extent of auditing established by the DSMC using NIH guidance, is dependent upon many factors including the risk and the level external monitoring and/or auditing. 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 risk and the corresponding auditing frequency for the study.

Procedures for DSMC Review of Protocol Compliance

A major function of the Committee is reviewing the outcome of DOCM audits and providing guidance on necessary actions. The purpose of these reviews is to ensure that research conducted in the ACC adheres to the highest standards for safety, quality and compliance, 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 quality control and quality assurance review by the DOCM 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 CTSRMC and DSMC.

Do —Implementation of the process. This is achieved through PI adherence to their MP, and DOCM selection of studies and subjects for auditing.

Check —Measuring progress and checking against expectations. Checking is done through PI monitoring per the MP, and DOCM audits on behalf of the DSMC.

Act —Analyzing the information provided during the check process and determining where to apply changes that result in improvement. The Appropriate actions are taken to correct deficiencies and this is incorporated into either the Institutional DSMP or study MP as applicable.

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 auditor will be evaluated by the DSMC 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 (not differences in opinion) in the audit report. All responses to audit 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 has been received or the response window has passed without a PI response.

Minor Deficiencies

Minor deficiencies are defined individual deficiencies that do not impact endpoint data quality, subject safety and/or integrity of the study. Although one or two minor deficiencies may not impact endpoint data quality, subject safety or study integrity, numerous minor deficiencies, especially those of the same type may, therefore, too many minor deficiencies could turn into moderate or major deficiencies.

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 endpoint data quality, overall study data integrity, or identify process problems. Deficiencies that affect endpoint data quality should appear in less than 15% of the sampled data and less than 25% of other study data. Greater than 10% and 25% respectively, 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 requires a copy of the plan or request details of the plan be included in their response to the audit letter. The findings may warrant an unscheduled re-audit of the study at the discretion of the DSMC Director or DSMC. The PI is given thirty business days to respond to these finding. An evaluation of the deficiencies will be re-evaluated upon receiving the PI's response or the response window has passed without a PI response.

Major Deficiencies

Major deficiencies are defined by the DSMC as those that impact more than 15% of endpoint data quality, more than 25% of overall study data integrity, impact safety and/or integrity of the study, show patterns of operational and systemic failures, or indicate that the PI is not appropriately overseeing the study. The PI will be given 15 business days (may change at the discretion of the DSMC) to respond to the letter for the final

determination of the deficiencies. Once the PI responds to the audit letter, if a study is determined to have major deficiencies resulting in a DSMC mandated study hold or closure, the IRB 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 fifteen business days to respond to these findings including development and implementation of a Corrective Action Plan (CAP). An evaluation of the deficiencies will be re-evaluated upon receiving the PI's response and CAP and DOCM auditors will provide guidance and suggestions to the study team to help them during the corrective action process. The findings will warrant a re-audit of the study within sixty days of the audit response due date, or sooner 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. If a DSMC mandated hold is placed on the study, once the DSMC determines that the study and/or study team have achieved an acceptable level of quality, the DSMC will notify the IRB that the deficiencies have been corrected, training has been completed, processes have been restructured and the PI and his/her team are allowed to 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 notify the IRB and determine if the the deficiencies should be reported to the NCI/NIH, FDA or other regulatory body. Any action resulting in a mandated temporary or permanent suspension of an NCI-funded clinical trial or trial investigator will be reported by e-mail or phone to the NCI Program Director responsible for funding the trials, and other appropriate agencies within 48 hours of the suspension. The Program Director will be updated as requested on the progress of corrective actions until all issues are satisfactorily resolved/addressed. The final disposition of the corrective actions will be provided to the Program Director in writing.

PI Response to Audit Letter

The findings on the audit form will be incorporated into a letter which will be sent to the PI with a deadline for response. At its discretion, the DSMC may ask the DOCM to provide a copy of monitoring/audit letters to Department Chairs or the Cancer Center Director.

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 made by the PI in writing, explain the need for the extension and provide a date the response will be received. Extensions of no greater than ten business days may be granted. 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 a response is received and accepted by the DSMC

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 on in-house studies, or EPR funded studies that are conducted solely in the ACC (includes ACC multi-site studies). 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 PennCTMS (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) and all other events in aggregate on a monthly basis. 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 or other entities as necessary.

Reportable Events

The DSMC's requirements for AE submission differs from the IRB because the goal of AE review is different. The DSMC requires AE submission for in-house studies or EPR funded studies that are conducted solely in the ACC (includes ACC multi-site studies) as follows:

On-Site subjects (this includes any subjects enrolled at other sites on an ACC multi-site study)

1. All grade 3 or higher events regardless of attribution or expectedness within 10 business days of knowledge.
2. All unexpected deaths within two business day of knowledge.
3. All others deaths within 30 days of knowledge. Deaths of subjects greater than 90 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

Studies receiving only funding/drug from a pharma/biotech company are not "fully sponsored" and events must be reported per DSMC requirements.

Studies sponsored by other academic centers, government agencies, foundations, consortia, etc. qualify for DSMC reporting I they do not have a central body reviewing AEs.

Reportable AE Details

Every effort should be made to report an event as a **diagnosis**, not as a list of symptoms. Symptoms that led to the diagnosis should be included in the event description, but should not be the actual event.

Once an event is reported, you must keep the information accurate and current in Velos. If new/updated information is learned about the event, the event a new Follow-Up report should be created. The original report should not be deleted.

The PI should ensure that the outcome of an event is not being recorded as the event, for example "hospitalization". An AE cannot be hospitalization, the event is what led to hospitalization. Hospitalization is an outcome.

Death can be both an event and an outcome so it is vital that the PI determines what caused the event of death and grades the cause of death as a grade 5 (i.e. grade 5 respiratory failure), then reports death as an individual report with its own start date and specific details.

If there were typos or other significant mistakes in the original report (not new information or clarification or previous information), then the report should be corrected promptly.

All AEs should include grade, attribution and expectedness as determined by the PI or sub-I. Only an investigator may determine the diagnosis, attribution and expectedness. PIs must confirm grade.

For attributions of "unrelated", an alternative explanation must be provided to explain to what the event is being attributed.

For studies using multiple agents in a single study, the agent to which the event is being attributed should be identified.

Deaths related to disease progression must clearly state that fact in the report.

The DSMC reserves the right to modify the reporting requirements for studies of specific interest.

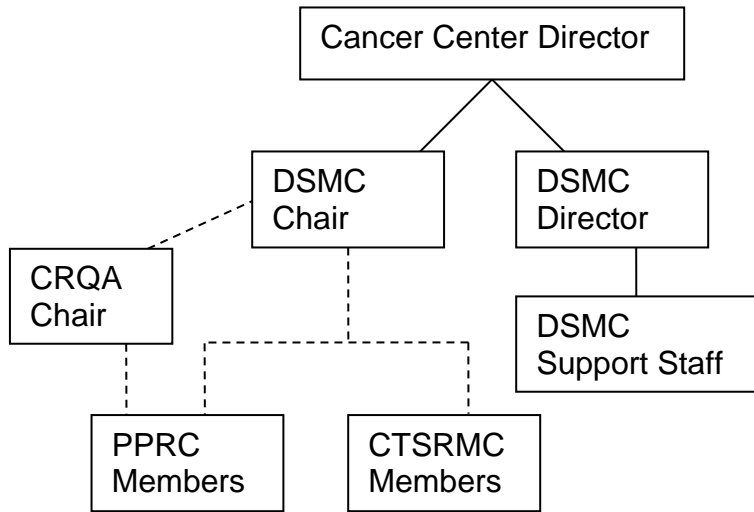
Reporting Events

All events must be entered into the ACC Clinical Trials Management System (CTMS using the centralized reporting form. This form was developed by the DOCM and contains all of the elements required by

regulatory agencies and the DSMC 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. DSMC Coordinators review imported events against the medical records and will query study teams for additional details to ensure that the reports generated for the DSMC are high quality. The PV database is updated with details that cannot be included in traditional AE reporting. These details facilitate DSMC review. Reporting events outside of the CTMS or responses to queries should be sent via the listserv to DSMC_AE@lists.upenn.edu.

Further details about AE reporting can be found on our website www.ctsrmc.org/sae.php

DSMC STRUCTURE



DEPARTMENT OF OPERATIONS, COMPLIANCE AND MONITORING (DOCM)

Overview of the DOCM

The DOCM is the central department within the ACC that oversees all research conducted within the center regardless of the type of intervention or sponsor. The DOCM also operationalizes and supports the activities of the CTSRMC and DSMC; sets the standards and policies for center-wide research operations; manages the cancer-aspect of the Penn CTMS (Velos eResearch); manages data reporting to the NCI; provides training for ACC researchers and their team members; and is responsible for the Regulatory Affairs of the ACC. To ensure the needs of the entire ACC are met without bias or influence, the DOCM Director who also serves as the ACC Chief Compliance Officer for Clinical Research, reports directly to the Cancer Center Director.

Protocols are audited by the DOCM based on the risk assigned to the study and the policies of the DSMC. The purpose of these audits is to evaluate protocol compliance, data integrity and to ensure that all cancer-related human subject studies are conducted in accordance with all federal 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 the CHOP Center for Childhood Cancer.

Auditing by Sponsor Type

The extent of auditing conducted by the DOCM is based on the standards defined by the DSMC and the risk assigned at the time of CTSRMC approval. All protocols considered to be part of the ACC portfolio must have some level of CTSRMC review, therefore, protocols that are not reviewed by the CTSRMC will not have access to DOCM support and oversight. For example, An ACC investigator holds an IND but the protocol will not enroll Penn subjects and no protocol-related activities will be conducted at Penn.

- **In-House-** These studies are audited by the DOCM as required by the risk level assigned by the CTSRMC.
- **Other Externally Peer Review Sponsored- EPR studies can fall into two categories:**
 - 1) Penn investigator initiated with funding from an EPR agency (see list on our website www.ctsrcmc.org for qualifying entities; or
 - 2) ACC investigator participating in an EPR study funded at another site.Studies in the first category are treated and audited like in-house studies. Studies in the second category are treated and audited like in-house unless the study has an oversight body that monitors/audits the study at least once a year.
- **NCI Cooperative Groups and Pharmaceutical/Biotechnical Industry-** Because these sponsors have approved oversight programs, the DOCM does not audit cooperative group protocol unless there is a for-cause need or unless the PI has asked for the study to be part of the DOCM External Inspection Support program.
- **Pharmaceutical/Biotechnical Industry-** Because these sponsors have approved oversight programs, the DOCM does not audit cooperative group protocol unless there is a for-cause need or unless the PI has asked for the study to be part of the DOCM External Inspection Support program.

Auditing Timelines

- **High risk** protocols are the top priority of the ACC and are audited 3-6 months from the first subject enrolled and approximately every 3-6 months thereafter until all subjects have completed all protocol obligations. This schedule may be changed at the discretion of the DSMC. High enrolling or quick enrolling studies will be audited more frequently as necessary. 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 approximately 30 business days of the audit. The Committee may alter the frequency of auditing 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.
- **Moderate risk** protocols are audited approximately twelve to eighteen months from the first subject enrolled and every twelve to eighteen months thereafter for the duration of the study only if DOCM auditors are current on all high-risk audits, Prospective Compliance Assessments and External

Inspection Support tasks. The DOCM may also be requested to audit a specific moderate risk protocols at the discretion of the DSMC.

- **Low risk** are only audited on a for-cause basis at the request of the PI, DSMC or ACC Director.

Once an 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 NCI, the FDA and the University expect that studies are maintained in a high quality manner as the study progresses therefore a five-week notice is considered more than sufficient to prepare for an audit.

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 (screening, 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.
 - All inclusion are documented
 - All exclusion are documented
- Treatment administration and accountability
 - Source documents of orders, dispensation and administration. Administration records should contain up/down times or overall time of administration, date, dose, height and weight (if applicable to dose calculation). 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 should be documented as with a final diagnosis as much as possible, 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 (where applicable)
- Overall organization of the study, PI oversight, appropriate delegation, appropriate training, and study related knowledge of staff
- Manufacturing (where applicable)

Electronic Versions of Source Documents

If any of the above documentation is maintained in electronic form that is not accessible to the auditor, access must be arranged at the time of the audit so that the auditor can review such records. Also, memos should be placed in the study binder indicating where the electronic source can be located. If the auditor is not given access to these documents at the time of the audit, the missing information will be recorded as deficiencies. The study team is responsible for ensuring the auditor has all records pertaining to the conduct of the study at the time of the audit.

Auditing Multi-Site Protocols

DOCM auditors no longer audit non-Penn study sites due to the logistics and cost of travel; complications with remotely accessing systems located at other sites; institutional limitation at other centers in regards to providing documents and data for remote monitoring and the changing IT landscape that results in remote sites changing agreements as their institutions change policies. Therefore, it is the PIs responsibility to monitor/audit all external sites commensurate with study complexity. There must be at least once visit to the study site to review electronic source systems. PIs may use experienced members of their study team, or hire an external monitoring entity to serve in this capacity. Details of the PIs monitoring must be fully and clearly documented in the Multi-site MOP. Investigators are bound by the MOP.

HIPAA

Every audit includes evaluation of HIPAA compliance in accordance with the CTSRMC and IRB approved HIPAA Authorization Form. The auditor reviews the study documents to confirm, as much as possible, 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.

GMP

The DOCM uses the standard regulatory checklist for GMP (*visit our website www.ctsrmc.org for details*), 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 (*visit our website www.ctsrmc.org for details*), 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 (*visit our website www.ctsrmc.org for details*) 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.

Research Pharmacy

The DOCM conducts facility inspections of the Research Pharmacies as necessary. These inspections are not the same as agent accountability during study monitoring/auditing. Inspections of the Research Pharmacy include (not limited to) a review of randomly selected studies, SOPs, and environmental controls. (*visit our website www.ctsrmc.org for details*)

Data Confidentiality

Although DOCM monitors are considered covered entities of the institution, all reasonable efforts are made ensure data confidentiality is maintained. Subjects are only identified by ID# and initials. Electronic data systems are accessible only by password protected access with an audit trail. Treatment arm randomization blinding information is not made available to the auditor. This information is maintained by the Biostatistical

Core and /or the Investigational Pharmacist and is never associated with the study to avoid unintentional unblinding.

DOCM Role in External Audits/Inspections and Audit Readiness Support

In addition to auditing studies, the DOCM provides two optional support services to investigators to help them initiate and maintain their studies in a state of high quality and audit readiness. "Audit readiness" as used specifically in this section applies to the concept of being prepared for monitoring, auditing and inspection by either the ACC DOCM, industry sponsors, national cooperative group, NIH, NCI, CTEP, and the FDA. One service is Prospective Compliance Assessments (PCA) and the other is External Inspection Support (EIS).

- **Prospective Compliance Assessments**

- The PCA program is available to all ACC investigators. The program is limited to the following studies:
 - Any study that qualifies as high risk based on the risk table above
 - Any study that qualifies as moderate risk unless it is part of another University oversight program.
 - Any industry sponsored Ph I, II or III study if:
 - The PI was/is a major contributor to the science or design
 - The PI is the national leader of the study
 - The study is part of an accelerated approval program
 - The study is likely to support a marketing application
 - Any NCTN Cooperative Group or CTEP sponsored studies
- **This support functions should be requested prior to the study opening to enrollment but absolutely no later than the first two subjects enrolled. Investigators seeking support outside of these criteria will be declines, but still have access to EIS.**
- The study investigator must complete, sign and date the Prospective Compliance Assessment request form. (*visit our website www.ctsrmc.org for details*).
- The DOCM will assess the study for appropriateness for the PCA program and notify the investigator that the request has been accepted.
- Any study accepted into the PCA program is automatically part of the EIS program unless the PI specifically opts out of EIS.
- Once accepted into the PCA program, the investigator and study team will be contacted by DOCM staff to schedule an initial planning meeting. Following the meeting, the DOCM staff will provide the investigator with a guidance document that details the approach to audit readiness and how to keep their study documents (subject and regulatory) organized and current. This guidance may also include other details specific to the study. In addition, a calendar outlining the time of the first assessment and then each follow-up assessment will be provided. This calendar will be adjusted by the DOCM as needed.
- If the study team fails to comply with the schedule and/or does not maintain a state of audit readiness, the DOCM will remove the study from the PCA program. Studies removed from PCA cannot re-enter.
- Assessments are not formal audits so issues identified during assessments will be relayed to the study team via e-mail within five business days of the assessment. DOCM staff will work with the study team if necessary to help them make adjustments or to evaluate changes implemented to ensure that the changes are keeping the study team on track. This process will continue until all subjects have completed study obligations. If subjects are put into long-term follow-up, DOCM staff will continue to assess the subject for one year, not throughout survival.

External Inspection Support (EIS)

- The EIS program is available to all ACC investigators. The program is limited to the following studies:
 - Any study that qualifies as high risk based on the risk table above
 - Any study that qualifies as moderate risk unless it is part of another University oversight program.
 - Any industry sponsored Ph I, II or III study if:
 - The PI was/is a major contributor to the science or design
 - The PI is the national leader of the study

- The study is part of an accelerated approval program
- The study is likely to support a marketing application
 - Any NCTN Cooperative Group or CTEP sponsored studies
- Investigators are encouraged to apply for EIS as early in the study activation process as follows (preferably through the PCA program).
- The study investigator must complete, sign and date the EIS request form. (*visit our website www.ctsrmc.org for details*).
- The DOCM will assess the study for appropriateness for the EIS program and the level of EIS support that will be provided based on the following:
 - Studies **will not** be accepted into the program if:
 - the study site has already been closed-out by the sponsor;
 - if a marketing application submission is pending within 90 days of EIS request;
 - if a sponsor has already notified the site that they have submitted a marketing application;
 - if the FDA already has notified the site of an intent to inspect.
 - If the DOCM accepts a study into the EIS program and is notified within the first 90 days of assessing the study that an inspection is scheduled, DOCM staff support will be limited to advising and guiding during preparations and being available to the team to answer questions during the inspection.
- If accepted into the EIS program, the investigator and study team will be contacted by DOCM staff to schedule an initial assessment of the state of the study. This assessment must take place within 10 business days of DOCM staff request.

Scope of EIS Support

- For studies that have not yet activated or have fewer than two subjects, the DOCM will follow the PCA process identified above. In addition, at the time an external audit/inspection notification is received:
 - The DOCM will assist the PI with preparation for external inspections and will help the team manage the inspection, or will fully manage the inspection at the discretion of the ACC Chief Compliance Officer for Clinical Research and the DSMC Chair.
 - Following the close-out of the inspection, DOCM staff will work with the study team to address issues identified during inspections.
 - The DOCM will work with the study team to implement corrective actions deemed necessary following an inspection.
- For studies that have enrolled more than two subjects at the time of the request:
 - The study team must have retrospectively organized the study documents per the DOCM guidance (*visit our website www.ctsrmc.org for details*) and performed a preliminary assessment of the documents to ensure completeness of the records.
 - DOCM staff will conduct an audit no later than five business days from the request.
 - One full subject chart, randomly selected by the DOCM auditor will be reviewed
 - A random selection of Informed Consent Forms will be reviewed
 - A random selection of regulatory documents will be reviewed
 - Biospecimen chain of command records will be reviewed (if applicable)
 - Pharmacy records will be reviewed (if applicable)
 - Subject self-administration records and compliance will be review (if applicable)
 - Supporting documentation of the CHPS unit of other supporting entities will be reviewed (if applicable)
 - Assessments are not formal audits so issues identified during assessments will be relayed to the study team via e-mail within five business days of the assessment.
 - If the study is determined to meet DOCM requirements, the PI will be formally notified that the study has been accepted into the program.
 - A calendar outlining each follow-up assessment will be provided. This calendar will be adjusted by the DOCM as needed.
 - If the study team fails to comply with the schedule and/or does not maintain a state of audit readiness, the DOCM will remove the study from the EIS program. Any study removed from the program cannot re-enter.

- DOCM staff will work with the study team if necessary to help them make adjustments or to evaluate changes implemented to ensure that changes are keeping the study team on track. This process will continue until all subjects have completed study obligations. If subjects are put into long-term follow-up, DOCM staff will continue to assess the subject for one year, not throughout survival.
- At the time an external audit/inspection notification is received (See External Audit Announcement guidance):
 - DOCM staff will meet with the study team and give guidance on what needs to be done to prepare for the inspection and to review any areas of concern.
 - DOCM staff will communicate with the study as they prepare to guide them as needed.
 - The study team will fully manage the inspection. DOCM staff will be available to the study team during the inspection to answer questions and/or provide support.
 - Following the close-out of the inspection, DOCM staff will work with the study team to address issues identified during inspections.
 - DOCM staff will work with the study team to implement corrective actions deemed necessary following an inspection.

DOCM PCA and EIS for NCTN Cooperative Group Audits

All of the requirements identified in the PCA and EIS sections above apply to NCTN Cooperative Group audits. However, at the time of an audit/inspection, the ACC has an NCTN Coordinator who must also be involved every step of the way throughout the process.

- The NCTN Coordinator is responsible for working directly with the study team(s) to help them prepare their studies for DOCM assessments and working with the team to address areas of concern identified by DOCM auditors.
- The NCTN Coordinator is responsible for managing audits and working with the study team and DOCM staff (if needed) throughout the audit to address concerns and respond to questions.
- The NCTN Coordinator will draft the site response to audit finding and provide to the DOCM Director of Compliance for final review and approval.
- The NCTN Coordinator will work with study teams post-audit to implement corrective actions.

DOCM PCA and EIS for CTEP and NCI/Theradex Audits

- **CTEP-** Study teams participating in any CTEP funded or supported studies must notify the DOCM before the study activates. CTEP funded/supported studies **MUST** be enrolled in the PCA program. Any CTEP funded/supported study that is not enrolled in the PCA prospectively, will be enrolled retrospectively. The study team will be required to follow the DOCM Audit Readiness process. (*visit our website www.ctsrmc.org for details*)
- Because CTEP inspection can include multiple protocols and multiple PIs from many areas of the ACC at one time, and the outcome of these audits can heavily impact the entire ACC, the DOCM will fully manage the audit
- Following the close-out of the inspection, DOCM staff will work with the study team to address issues identified during inspections.
- The DOCM will work with the investigators to respond to audit findings
- The DOCM will work with the study team to implement corrective actions deemed necessary following an inspection.
- NCI/Theradex- These audits can include CTEP and NCTN studies can include multiple protocols and multiple PIs from many areas of the ACC at one time, and the outcome of these audits can heavily impact the entire ACC, the DOCM will fully manage the audit with a hybrid approach:
 - If the list of studies selected by the NCI/Theradex include NCTN Cooperative Groups, the DOCM will involve the NCTN Coordinator with the preparation of NCTN studies.
 - The DOCM will fully manage the audit but require the NCTN Coordinator to work closely with the department to address NCTN specific issues.
 - Following the close-out of the inspection, DOCM and NCTN Coordinator (if applicable) staff will work with the study team to address issues identified during inspections.

- The DOCM and NCTN Coordinator (if applicable) will work with the investigators to respond to audit findings
- The DOCM and NCTN Coordinator (if applicable) will work with the study team to implement corrective actions deemed necessary following an inspection.

Information Managed by the DOCM

In addition to providing an auditing function for the DSMC, the DOCM also centrally manages all off the ACC data related to protocol and subject registration, reported AEs, and data for the NCI Clinical Trials Reporting Program. Data are tracked and queried to assure compliance with NCI requirements for Designated Comprehensive Cancer Center.

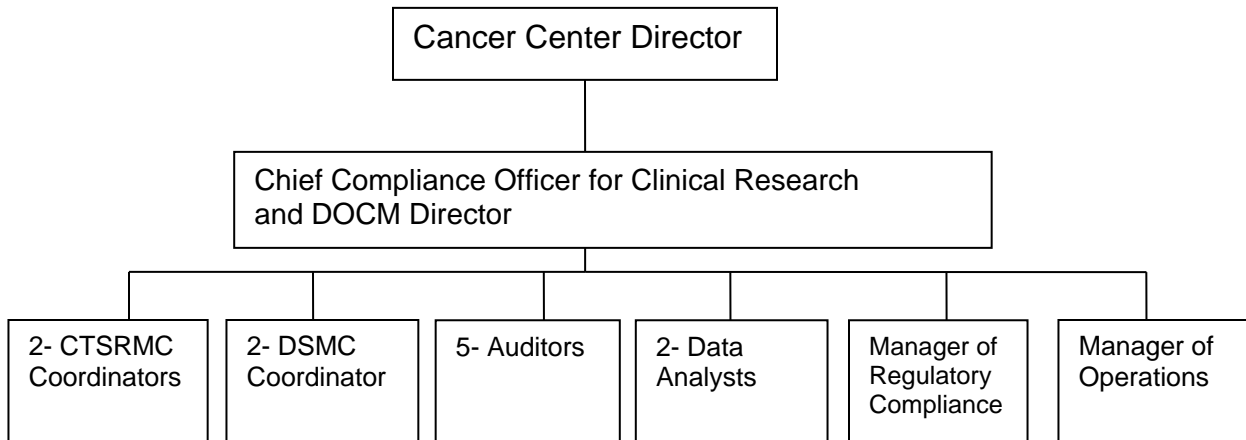
CTSRMC

- Study status updates to ANY study must be immediately applied in Velos.
 - The definitions for, and use of the various statuses can be found on our website www.ctsrc.org
- A copy of the IRB Continuing Review must be sent to the CTSRMC for all studies that have been approved via the full-committee process.
- Publications for all studies that have been approved via the full-committee process
- All subjects must be registered in Velos within 48 hours of being enrolled on the study.
 - The definitions for, and use of the various subject statuses can be found on our website www.ctsrc.org
- Subject statuses must be updated as the subject moves through the study.
- The NCI CTRP requires the ACC to provide specific pieces of data related to subjects. Please see our website www.ctsrc.org for specifics.

DSMC

- The DSMC should be immediately notified of trials suspended due to safety issues.
- Protocol exceptions requests or reports of applicable deviations should be made via the DSMC listserv DOCM_Compliance@lists.upenn.edu
- AEs and SAEs that meet the DSMC requirements for reporting must be promptly entered in Velos.
- DSMB, Medical Monitoring of Safety Monitoring Committee Reports
- Any correspondence from sponsors or regulatory agencies regarding safety or study design issues for protocols approved by the CTSRMC via the full-committee process.

DOCM STRUCTURE



Responsibilities of the Principal 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.

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

- Delegated authority must be consistent with the education, licensing, training and experience of each individual.
- The PI may not delegate the role of PI.
- The PI may not delegate authority to positions that require licensing (e.g. nurses, NP, PA, pharmacy, MA, etc.) that are outside the boundaries of licensing (locally, federally or institutionally).
 - The PI is responsible for understanding licensing boundaries in Commonwealth and at Penn.
- The PI may not delegate any study related tasks to individuals who are not part of the study team.

Additional Institutional 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.

University of Pennsylvania Institutional Review Board (IRB) and the CHOP IRB

The University of Pennsylvania and CHOP IRBs review all research involving human subjects at the University of Pennsylvania for ethics, subject safety and equipoise. The IRB ensures that research meets ethical standards and is conducted according to federal, state and local regulations. IRB review is completely independent of the CTSRMC/PPRC without any overlap. Consistent with NIH requirements and FDA guidance, Penn's IRB has entered into collaborative agreements with the NCI CIRB and multiple commercial IRBs to allow harmonized review of multi-site studies which and improve time-to-activation. No cancer related protocol can receive full approval from the Penn or CHOP IRB without CTSRMC approval.

Unlike the Penn and CHOP IRBs that will hold study consents until documentation of CTSRMC/PPRC approval is granted, the NCI CIRB and commercial IRBs have not agreed to provide such firm barriers to opening. Instead the NCI CIRB and commercial IRBs remind investigators that they must continue to comply with all other governmental, local and institutional policies. CTSRMC/PPRC approval (of equivalent per CTSRMC/PPRC policies details above) is mandated for all cancer-relevant research at Penn. Failure to comply with this policy may result in study closure and mandatory corrective actions.

University of Pennsylvania Schools

- **Perelman School of Medicine (PSOM) Office of Clinical Research (OCR)**

For ACC studies with faculty members in the PSOM, an additional oversight body exists. OCR represents centralized PSOM policies and requirements for its faculty members, of which some are also ACC investigators. The ACC DDCM and PSOM OCR are separate oversight entities. However, the ACC DDCM works collaboratively with OCR to help the PSOM to accomplish common goals.

- **Other Schools**

As other Schools implement more centralized robust research infrastructure, the DOCM will work collaboratively with each school to accomplish common goals.

CHOP Research Institute

For ACC studies at CHOP, investigators an additional oversight body exists. The CHOP Research Institute represents centralized Institute policies and requirements for its members, of which some are also ACC investigators. The ACC DOCM and CHOP Research Institute are separate oversight entities. However, the ACC DOCM works collaboratively with CHOP to help the PSOM to accomplish common goals.

Technologies

Website (www.ctrsmc.org)

The DOCM has 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 the ACC research blog. The website changes often with new content and feature. The ACC community is encouraged to visit the website often.

- **Forms and Guidance Documents**

All form, guidance and policies reference in this document can be found on our website. Please check the website often for policy, guidance and form updates to ensure you are following the most current process.

DOCM Custom Applications

The DOCM has multiple custom application that were designed specifically to meet the data collections and reporting needs of the CTRSMC, DSMC and DOCM. These applications capture data specific to the functions of each entity. These applications were designed by the DOCM Director and developed and managed by the Database and Applications Group (DAG). The functionality of these applications continue to grow to enable dynamic data visualization and performance tracking.

PennCTMS (Velos)

All cancer-related protocols and the protocol enrolled subjects must be registered in the system. Velos is now enterprise-wide in the Perelman School of Medicine (PSOM) with special content to ensure ACC needs are met. The PSOM CTMS management team works collaboratively with the DOCM Director when system changes (upgrades, bug patches, etc) may impact the ACC, and to ensure that ACC identified needs are met in a timely manner.

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. Level of access and training needs are identified by the DOCM.

Administrative Information

Further Guidance

NIH policy (<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>) with additional description at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>) requires that grantees have in place procedures for DSM of clinical trials. This is to insure the safety of participants, the validity of data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be concluded successfully.

FDA:

www.fda.gov

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