Abramson Cancer Center of the University of Pennsylvania

Institutional Data and Safety Monitoring Plan (DSMP)

v.4.1_20240402

the cure is within
ABRAMSON CANCER CENTER

Children's Hospital of Philadelphia®
Cancer Center

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Full AAHRPP Accreditation

TABLE OF CONTENTS

SECTIONS	PAGE
Introduction	3
Institutional and Study Specific Monitoring Plan	3
Principles Used to Guide the Development of the ACC Institutional DSMP	3
Auditing versus Monitoring	4
ACC Risk Categories for Studies	5
Clinical Trials Scientific Review and Monitoring Committee (CTSRMC), Pediatric Protocol Review Committee, Disease Team/Focused Groups	6-25
Data and Safety Monitoring Committee (DSMC)	26-36
Department of Operations, Compliance and Monitoring (DOCM)	37-48
Responsibilities of the Principal Investigator (PI)	49
Additional Oversight	49-50
Technologies	50-51
Administrative Details	51

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 Once Cancer Clinical Research model which includes twelve University Schools, all Penn-owned hospitals and 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 the NCI, FDA, HHS and the needs of the ACC. The ACC has approached human subjects 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 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 of 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 involves unblinding/unmasking, 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 several 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

Auditing: 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).*"

Monitoring: 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 evaluates study conduct, compliance and quality through auditing. Monitoring is conducted on two levels. PIs are responsible for oversight through monitoring consistent with standard PI oversight responsibilities. PI oversight is detailed in the Monitoring Plan template included with every new submission to the CTSRMC, or in custom Monitoring Plans developed by the PI and the DOCM for studies that include Enhanced Auditing or Prospective Compliance Assessments (ProCAP). Sponsors are responsible for monitoring consistent with federal Sponsor oversight responsibilities.

The CTSRMC requires protocol submissions to include a PI Monitoring Plan (MP) that must be followed by the study team for the duration of the study. This plan should complement any plans developed by study sponsors (where applicable) and must utilize 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 protect the safety of subjects and the validity and integrity of 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
• Biospecimen collection/banking • Residual collecting • Retrospective chart reviews • De-identified genetics studies • Survey/Questionnaire • HUD protocols • Database registry protocols
LOW RISK
• 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 and provides monitoring.
MODERATE RISK
• EPR funded intervention studies that are not intended to treat cancer or conditions related to a cancer diagnosis. • 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.) • Identified genetics studies. • Any study that is independently monitored by a sponsor or a sponsor-designated qualified contractor. Monitoring letters must be provided to the DOCM.
HIGH RISK
• Any In-house or investigator-initiated trial intended to treat cancer or conditions related to a cancer diagnosis (with or without a faculty held IND/IDE) that is not routinely monitored by entities outside of the ACC. • All NCTN studies • Any interventional study that uses agents manufactured on campus that is not routinely monitored by entities outside of the ACC. • Cancer treatment trial with provisions to waive consent in emergency circumstances. • Involves enrollment of vulnerable population(s)

NOTE: Oversight provided by an external sponsor does not modify or eliminate the need for investigators to oversee, in an ongoing manner, the conduct of their research and follow the Monitoring Plan template (MP) submitted to the CTSRMC/PPRC as part of gaining initial approval.

CLINICAL TRIALS SCIENTIFIC REVIEW AND MONITORING COMMITTEE (CTSRMC)

Overview of CTSRMC

The Abramson Cancer Center (ACC) has an established Protocol Review and Monitoring System (PRMS) comprising first-stage review by the Disease Team/Focused Group and then second-stage full scientific review by the Protocol Review and Monitoring Committee known as the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) which was established in 1992 and has been continuously approved by the NCI. The CTSRMC's focus is scientific merit, prioritization, feasibility, inclusiveness, statistical design and ongoing progress of cancer relevant protocols conducted within the University of Pennsylvania and Children's Hospital of Philadelphia (CHOP). Pediatric protocols are reviewed by an expert Sub-committee of the CTSRMC known as the Pediatric Protocol Review and Monitoring Committee (PPRC) which is based at The 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. Presented below is an overview of the PRMC as administered by the CTSRMC.

In 1997 The Vice Provost for Research and the Dean of the Perelman School of Medicine affirmed the Committee as the required body within the Perelman 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 the 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 not play a role in the scientific review process and does not influence any of the Committee's decisions. The CTSRMC/PPRC is ultimately responsible for the scientific review of protocols and has the sole authority to approve and authorize activation of clinical studies. The CTSRMC/PPRC is responsible for review not only of each protocol but of how each protocol complements the overall trial portfolio of the Center. The CTSRMC/PPRC is responsible for continuing review of open protocols, including accrual, new safety information, and scientific relevance, and has sole authority to close trials for these reasons. Final CTSRMC/PPRC decisions related to approval or closure may not be appealed.

Consistent with NCI Core Grant guidelines, the protocol review process must be done in two steps.

STEP ONE is a protocol acceptance review that must be done by a Disease Team/Focused Group (DT/FG). DT/FG are multi-disciplinary, organized by tumor histology or treatment modality, and are the first step in the development of the ACC clinical research portfolio.

- Step One review provides documentation of the process, criteria, and prioritization used by Disease Team/Focused Groups (DT/FG) for choosing which clinical trials will best serve the ACC catchment and patient populations as well as support the clinical and scientific goals of the team/group.
    - A DT/FG Review form was created to allow all DT/FG to capture all of the essential details necessary to perform a complete review, and to ensure consistency and standardization of review across the center. This form must be submitted with all protocols that the team/group recommends should move forward to CTSRMC/PPRC full-committee review.
    - Protocols will not be reviewed by the CTSRMC/PPRC without documented team/group approval.

- Teams/groups will maintain minutes of their meetings and a list of all protocols considered whether or not the protocol moves to full-committee review.
- CTSRMC/PPRC may request copies of such documents at its discretion.

STEP TWO is the CTSRMC scientific review of DT/FG acceptable protocols, which focuses on the scientific merit, statistical design, feasibility, competitiveness, ongoing accrual performance and scientific progress of cancer-related protocols. The CTSRMC must give reasonable consideration as to whether protocols under review have the potential to accrue participants of underrepresented populations, and other populations, in the Center's catchment area. Different levels of review exist based on the sponsor type, funding source, study populations and study design.

PRMC Reliance Agreements

For multi-site institutional trials at cancer centers with an NCI approved PRMC (scientific review committee), the PRMC 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 PRMC at the lead site be determined by the NCI to be conditionally acceptable or unacceptable, participating sites may select a single, acceptable PRMC at a participating NCI-designated cancer center to conduct the full scientific review.

Study teams are required to provide the CTSRMC/PPRC with documentation of protocol review and approval by another PRMC at the time of submission.

Study teams are required to provide proof that the PRMC 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.

DT/FG Members

Each DT/FG is led by a senior ACC faculty member who must be an experienced clinical trialist in the tumor histology/modality under review. Members represent a multi-disciplinary group of physicians as well as research nursing, infusion nursing, pharmacy, palliative care, health services, population sciences, nutrition and supportive care, study coordination, data management, regulatory coordination, biospecimen handling, DEI and individual CRU administrative leadership.

CTSRMC and PPRC Members

The CTSRMC and PPRC comprise 50 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 (not limited to) medical, radiation, and surgical oncology, head and neck cancer, pulmonary medicine, pediatric oncology, gynecological oncology, neurological oncology, cardio-oncology, cellular therapies, gene therapies, pathology, population sciences, and biostatistics. The Committee also has ad hoc expert members from Penn Environmental Health and Radiation Safety covering Radioactive Drugs and Biosafety. All 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.

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 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).

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

NCI-NCTN
Alliance for Clinical Trials in Oncology
- American College of Surgeons Oncology Group
- Cancer and Leukemia Group B

North Central Cancer Treatment Group
Children's Oncology Group
ECOG-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. This must be submitted with the study protocol.

Externally Peer-Reviewed
The NIH and all 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. As such, studies funded by these sources are considered Externally Peer Review (EPR) funded.

NIH Institutes
1. National Cancer Institute (NCI)
2. National Eye Institute (NEI)
3. National Heart, Lung, and Blood Institute (NHLBI)
4. National Human Genome Research Institute (NHGRI)
5. National Institute on Aging (NIA)
6. National Institute on Alcohol Abuse and Alcoholism (NIAAA)
7. National Institute of Allergy and Infectious Diseases (NIAID)
8. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
9. National Institute of Biomedical Imaging and Bioengineering (NIBIB)
10. Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
11. National Institute on Deafness and Other Communication Disorders (NIDCD)

12. National Institute of Dental and Craniofacial Research (NIDCR)
13. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
14. National Institute on Drug Abuse (NIDA)
15. National Institute of Environmental Health Sciences (NIEHS)
16. National Institute of General Medical Sciences (NIGMS)
17. National Institute of Mental Health (NIMH)
18. National Institute on Minority Health and Health Disparities (NIMHD)
19. National Institute of Neurological Disorders and Stroke (NINDS)
20. National Institute of Nursing Research (NINR)
21. National Library of Medicine (NLM)

NIH Centers

1. NIH Clinical Center (CC)
2. Center for Information Technology (CIT)
3. Center for Scientific Review (CSR)
4. Fogarty International Center (FIC)
5. National Center for Advancing Translational Sciences (NCATS)
6. National Center for Complementary and Integrative Health (NCCIH)

NIH Recognized Peer Review Funding Sources

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) 1
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. St. Baldrick's Foundation
26. Stand Up to Cancer (SU2C)
27. Susan G. Komen for the Cure
28. The California Breast Cancer Research Program (CBCRP)

29. The California Tobacco Related Disease Research Program (TRDRP)
30. 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

Other Funding/Support Sources
NIH National Trials Networks
Cancer Therapy Evaluation Program (CTEP) (non-NCTN trials)
Cancer Control Protocol Review Committee

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 and the investigator has full legal and regulatory responsibility for the study.

This category may also include:

- Studies authored and implemented by investigators at another Center in which the ACC is participating will be categorized as Institutional/In-house when:
    - The ACC investigator is not receiving financial support from the other center to conduct the study; and/or
    - The ACC investigator is a major contributor to the design and/or ongoing scientific progress of the study.

Industrial
A pharmaceutical/biotech company, another academic center, consortium, foundation, research group or similar that controls the design and implementation of these clinical research studies. The protocol is the full intellectual property of the company/institution, and the company/institution has full legal and regulatory responsibility for the study.

Investigator-Initiated Trials (IITs):
Those in which the primary intellectual contribution (conception, design, implementation, etc.) originated with a cancer center PI. For study source, they may be classified as Institutional, Externally Peer Reviewed, NCTN or even Industrial, if the center member was the intellectual source of the trial. Investigator-initiated trials can also include multi-institutional trials in which the center PI had a significant intellectual contribution, even if the trial originated with another institution.

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 prospective 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 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):** An intervention of a device product is being evaluated in a small clinical trial (generally fewer than 10 participants) to determine the feasibility of the product; or a clinical trial to test a prototype device for feasibility 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

Pragmatic Clinical Trials

A clinical trial that is designed to study a health intervention in a real-world setting that is similar or identical to the one in which the intervention will be implemented. Pragmatic trials are designed to evaluate the effectiveness of interventions in real-life routine practice conditions, whereas explanatory trials aim to test whether an intervention works under optimal situations. Pragmatic

trials produce results that can be generalized and applied in routine practice settings. Per NCI Implementation Science, "*pragmatic trials are often characterized by more lenient procedures and components of trials, where elements of the trial are meant to reflect "usual" contexts and populations in which and to whom the intervention would be delivered outside the context of the trial if shown to "work" in the trial. Results from pragmatic trials are meant to increase generalizability by designing the trial to mirror the situations in which the intervention would be delivered after the trial (pending supportive outcome data)."*

Multi-location and Multi-site Studies

Penn and CHOP fully own multiple institutions that may participate in clinical research. A study that is active at multiple owned facilities is categorized as multi-location. Studies that are active at multiple locations other than those that are fully owned are categorized as multi-site.

The Hospital of the University of Pennsylvania (HUP), Pennsylvania Hospital (PAH), Penn Presbyterian Medical Center (PPMC), Lancaster General Hospital (LGH), Chester County Hospital (CCH) in West Chester, Exton and Brandywine, and Penn Medicine Princeton Health (PMPH) are Penn-owned locations. The Children's Hospital of Philadelphia (CHOP) is an essential Penn partner and has long been formally part of the ACC core grant. As such, CHOP is also considered a participating location, and vice versa. CHOP Main Hospital, King of Prussia Middleman Family Pavilion and Voorhees Specialty Care & Surgical Center are CHOP-owned locations.
Any institution/center/facility not included above that participates in ACC research is considered to be an external site and such studies are categorized as multi-site. Some ACC studies may be a both multi-location and multi-site. In such cases, all of the multi-site requirements remain in effect for only the external sites. Specific details must be included in the study protocol and oversight plan.

Decentralized Clinical Trials (DCT)

The FDA has issued guidance in support of decentralization of clinical trials. This guidance is supported by HHS Secretary's Advisory Committee on Human Research Protections (SACHRP) and the NCI Clinical Trials and Translational Research Advisory Committee (CTAC).

FDA Guidance on Decentralization

Decentralizing clinical trials will allow some or all trial-related activities to take place at trial participants' homes or other convenient locations, instead of having them visit research sites. By reducing barriers to participation, we expect that DCTs will increase the breadth and diversity of participants in clinical trials and improve accessibility for those with rare diseases or mobility challenges. We anticipate that this approach will facilitate the development of drugs including in areas of medical need, resulting in more treatment options and improved patient outcomes.

Many clinical trials already include decentralized elements such that not all trial-related activities involving participants take place at traditional clinical trial sites. For example, laboratory tests are often conducted by clinical laboratory facilities at locations remote from traditional trial sites. DCTs have the potential to expand access to more diverse patient populations and improve trial efficiencies. Advances in clinical care using electronic communications and information technology to interact with trial participants in different locations (i.e., telehealth) allow for fewer in-person visits to clinical trial sites. Digital health technologies (DHTs), for example, have expanded the types of trial-related data that can be obtained remotely from trial participants. By enabling remote participation, DCTs may enhance convenience for trial participants, reduce the burden on caregivers, and facilitate research on rare diseases and diseases affecting populations with limited mobility or access to traditional trial sites. This may help improve trial participant engagement,

recruitment, enrollment, and retention of a meaningfully diverse clinical population. Fully decentralized trials may be appropriate for investigational products (IPs) that are simple to administer or use, have well-characterized safety profiles, and do not require complex medical assessments. Alternatively, hybrid decentralized trials may be more appropriate in cases where the administration of an IP or a complex medical assessment needs to be performed at a clinical trial site and some follow-up assessments could be performed remotely through online patient-reported outcome measures, via telehealth or in-home visits, or by local health care providers (HCPs), as appropriate.

Investigator-Initiated DCTs
The ACC supports and encourages the use of DCT design for appropriate studies, when feasible. Study investigators are encouraged to consult with the DOCM Director to determine if DCT is appropriate for their trial, and which DCT model- hybrid or full, is best. Specific details of the decentralization plan must be included in the study protocol at the time of submission to the CTSRMC. Decentralization may necessitate the development of additional study documents such as (not limited to) training materials, Manuals of Procedures, DEI recruitment plans and customized DOCM audit plans.

For DCTs conducted in a multi-site setting, the ACC PI must ensure the participating external sites are equipped to oversee DCTs at their location and must understand any restrictions on DCTs at the participating site that may impede participation.

Research Type:

These categories are used by the ACC to understand the impact of our research portfolio and are required by the NCI for reporting purposes.

- Treatment: 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 NCI guidelines.
- Non-Therapeutic Intervention- Studies in which the intervention is not intended to treat a disease, syndrome, or condition.
- Non- Intervention- Subject does not receive any intervention or treatment as part of the study design.

NOTE: When a study is registered with clinicaltrials.gov, the ACC will match, as much as possible, the category, purpose and research type with the categories in clincaltrials.gov.

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 Disease, Discipline and Focused Group Review form, 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.** Protocols submitted to the CTSRMC via the IRB's HSERA may encounter delays in review related to HSERA workflows outside the control of CTSRMC staff. **For the timeliest response and processing,** investigators are encouraged to submit a complete protocol packet to the CTSRMC via the CTSRMC listserve CTSRMC_SUBMISSIONS@LISTS.UPENN.EDU. This single site of submission significantly decreases the regulatory submission timeframe, allows multiple ACC review bodies to harmonize

and streamline their reviews and importantly ensures version control of key protocol documents. All of these efficiencies positively impact the time-to-activation.

Protocols must be submitted to the CTSRMC prior to, or at the same time as the IRB to avoid delays related to stipulations and related edits.

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.

Exemption Review

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 in the ACC CRMS (Velos)**, but no longer conducts scientific-peer review for merit, relevancy, feasibility, competitiveness, or prioritization.

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 CRMS (Velos)**.

In addition, protocols dealing with biobanks, development of databases, retrospective chart reviews and anonymized surveys/questionnaires also qualify for CTSRMC exemption. Administrative acknowledgement is usually issued within five 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.

- 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.

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.) Protocols utilizing such interventions must receive Full-committee review.

Expedited Review

- Studies conducted by NCI-sponsored NCTN, NIH National Trial Networks, and non-treatment trials that have received External Peer-Review (EPR) support are reviewed via expedited review. Per guidance from NCI staff, the CTSRMC reserves the right to change the level of review and/or issue stipulations that must be satisfied before the protocol can open to enrollment if serious safety concerns are identified or the committee believes the protocol cannot be conducted successfully as written. **Externally Peer Review Funded-** EPR studies are evaluated for local feasibility, prioritization and serious safety concerns. Per guidance from NCI staff, the CTSRMC reserves the right to change the level of review (require full committee review) and/or issue stipulations that must be satisfied before the protocol can open to enrollment if serious safety concerns are identified or the committee believes the protocol cannot be conducted successfully as written. Expedited review of EPR studies does not duplicate the external peer review process conducted at the time of funding review, which includes protocol design and statistics. Regardless of the type (treatment, non-therapeutic intervention or non-intervention) of study, once expedited approval is received, these studies are reviewed for accrual and scientific progress once opened to enrollment.
- **Compassionate Use/ Expanded Access**- Are 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. Once expedited approval is received, these studies are reviewed for accrual and scientific progress once opened to enrollment.

Protocols appropriate for expedited review may be submitted at any time and are reviewed by a Chair/Vice 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 CTSRMC/PPRC receipt, review and response is 20 business days.

Full-committee Review

All cancer treatment and other selected intervention studies, not included in the review categories above, require full-committee review.
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 regulatory and operations needs; discussion with the DOCM to develop an appropriate monitoring plan; review of the protocol submission packet with CTSRMC staff to make certain the submission is high-quality and complete.

CTSRMC meetings are held on the second and fourth Monday of every month. Additional details about CTSRMC meetings, requirements and processes can be found on the CTSRMC website www.ctsrmc.org.

Submission Deadlines:

A complete protocol packet may be submitted to the CTSRMC listserv CTSRMC_SUBMISSIONS@LISTS.UPENN.EDU when all required documents are finalized and signed. Complete submissions are added to the next available agenda.

If issues are identified by CTSRMC staff, related to protocol submissions packets, the submission will be returned to the team and an agenda time slot will not be held. All issues must be fully resolved by the study team prior to the submission being added to the agenda and assigned a review time.

Full-committee protocols are assigned to a primary reviewer with expertise in the targeted disease or modality, a secondary Chair reviewer and a biostatistical reviewer is assigned based on his/her statistical expertise. The CTSRMC Director, reviews all protocols for quality, inclusion of women/minorities, outreach plans and regulatory issues. Protocol review is not limited to reviewers assigned to the protocol. Feedback from all members is sought and encouraged. The average time from submission to review is 12 business days and a response from the CTSRMC/PPRC is usually received within 3 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.ctsrmc.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 10 business 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.

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, patient populations and center catchment, 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 video recorded transcript used in lieu of typed 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 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 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 provided to the University's IRB to facilitate the board granting final 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 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. Examples of 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.ctsrmc.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?

Inclusion
- The adequacy of plans to include subjects from all genders, racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed.
- Plans for outreach and engagement of disparate communities if applicable to the study
- Inclusion across the lifespan
- Are there unreasonable and/or unjustified exclusionary criteria that impede access for burdened or underrepresented populations?
- Plans for inclusion across the lifespan of the disease.

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)

The committee includes the Focused Group Review Form as part of the review and approval decision.

At the conclusion of the review the Committee votes on whether 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:

Priority Scores

The CTSRMC uses a modified version of the NIH Impact Score when assigning a priority score to individual protocols. The final score is determined by the assigned reviewers, Chairs and DOCM Director taking into consideration feedback from all members. The average of all reviewer impact/priority scores constitutes the final impact/priority score. Scores run from 1.0 to 3.0, where 1.0 is best.

1.0-1.9 (outstanding science, high priority, important)
2.0-2.9 (good science, lower priority, worthwhile,)
3.0-higher (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-Step CTSRMC/PPRC Review

Early in the development of their protocols, investigators may request a two-step CTSRMC/PPRC review to seek peer input on the purpose, design and statistical plan. The availability of this review process improve the quality of the protocol before it is submitted to both the CTSRMC/PPRC and IRB. This type of review 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. A list of recommendations/suggestions and other essential guidance is provided to the PI. PIs are strongly encouraged to implement the recommendations/suggestions before formal submission to the CTSRMC.

NOTE: Protocols submitted for Two-Step review must have been vetted for acceptance and prioritization by the DT/FG prior to being submitted.

CTSRMC/PPRC 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, enhanced auditing, multi-site support 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.ctsrmc.org for details)* with the study protocol. The CTSRMC reviews the justification request and determines whether the study should be opened outside the Cancer Center, the selected sites are appropriate and the PI has the experience and staff to 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. Such trials 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.

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 and that all necessary elements are complete.. 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 teams/focused groups and cancer center core grant programs. The CTSRMC/PPRC expects that all protocols that are submitted have been reviewed by the disease team/focused group 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 team/focused group leader. Protocols will not receive full approval until the Chair is satisfied with the proposed plan. Also, although EPR and NCTN protocols are not reviewed for scientific merit, they are reviewed for prioritization and competitiveness with other ongoing or proposed studies at our Center and thus are considered by the CTSRMC when assessing competition. Finally, the CTSRMC/PPRC assigned priority score is provided to each disease team/focused group and this score is to be used to prioritize projects within the team/group.

Justification and Prioritization (J&P) Form

The J&P form (*visit our website www.ctsrmc.org for details)* is where the PI formally provides to the CTSRMC/PPRC their justification for the specific study as well as other essential details about the study that are not contained in the protocol such as identifying their leadership role; for basket trials, identifying specific arms/cohorts of inclusion in the ACC; providing specific enrollment details for studies that are a combination of common tumors but include some rare sub-types; identifying publication plans and the like. Because the J&P form also captures NCI mandated data points, it must be submitted with all non-exempt protocols regardless of study source or sponsor. J&P forms may be completed a few months in advance of CTSRMC as part of regulatory facilitation, this creates the potential for stale data. PIs must ensure that the details in the J&P form are accurate at the time of CTSRMC submission. Inaccurate and/or stale information will cause delays in CTSRMC review and may impact approval.

Relationship of CTSRMC/PPRC and IRB

The CTSRMC and PPRC are separate and independent of 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. The NCI CIRB and commercial IRBs do not directly enforce this policy, however, all approvals include a statement that there may be other institutional policies governing final approval and activation of protocols and they remind PIs that they are responsible for complying with institutional policies such as those of the CTSRMC.

Time-to-Activation (TTA)

Protocol TTA begins with submission to the CTSRMC/PPRC. 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 regard 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 as well as resolving other administrative, financial and operational items. Regarding TTA, the Committees generally send initial review letters within 3 business days of the monthly meetings and respond to addressed stipulations within 10 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, amendment review and assessment 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. NOTE: 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.

RARE CANCERS: Per the NCI's MyPART - My Pediatric and Adult Rare Tumor Network, rare cancers are those that affect fewer than 40,000 people per year in the U.S. As a group, they make up just over a quarter of all cancers. A quarter of all cancer deaths each year are due to rare cancers. A list of rare cancers can be found at https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/about-rare-cancers

Because rates of cancer in children are very low, all children's cancers are considered rare.

- Accrual Monitoring- Studies are 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.
    - Special consideration is given to protocols that are experiencing low enrollment due to drug shortages, natural disasters, public health emergencies or have restrictions on the rate of enrollment such as competitive enrollment slots, and frequent holds for safety analyses since such models are outside of the PIs control but significantly impact the number of available enrollment slots and/or the rate at which subjects may be enrolled.
- Scientific Progress Monitoring- The ongoing review of amendments, modifications and administrative notifications allows the CTSRMC to track scientific progress on a continuum. Additionally, every protocol approved via full-committee is reviewed at least annually to assess whether or not the study is making appropriate scientific progress. The annual IRB Continuing Review, publications and additional documentation as applicable, for example, IND updates to FDA and DSMB reports are used to evaluate progress. 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 (MM)**

The ACC developed Medical Monitoring policy based on the NIH model. Medical Monitor will be a physician or other medically/scientifically qualified expert who is not directly involved in the trial and is not collaborating with the sponsor/investigator in any other trial. In the role, they may 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. Please visit our website (*www.ctsrmc.org*) for the plan and additional details. All high-risk investigator-initiated/in-house studies, studies involving on-campus manufacturing, studies involving waiver of consent must have a Medical Monitor assigned to the protocol. Medical Monitoring details must be included in the protocol at the time of submission and must utilize the ACC Medical Monitor policy.

- **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.ctsrmc.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. Certain high-risk studies, as seen in the ACC Risk table found on page 5 are required to have a DSMB detailed in the protocol at the time of submission

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.

- Disease Team/Focus Group Members COI
  DT/FG structures come with inherit conflicts, such as the Leader also being a PI or sub-PI. Conflict of Interest must be managed by DT/FG. DT/FG should have a conflict management plan. The AD for Clinical Research, Department Chair, Division Chief or other unconflicted leader may be part of the conflict management process.
- 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.

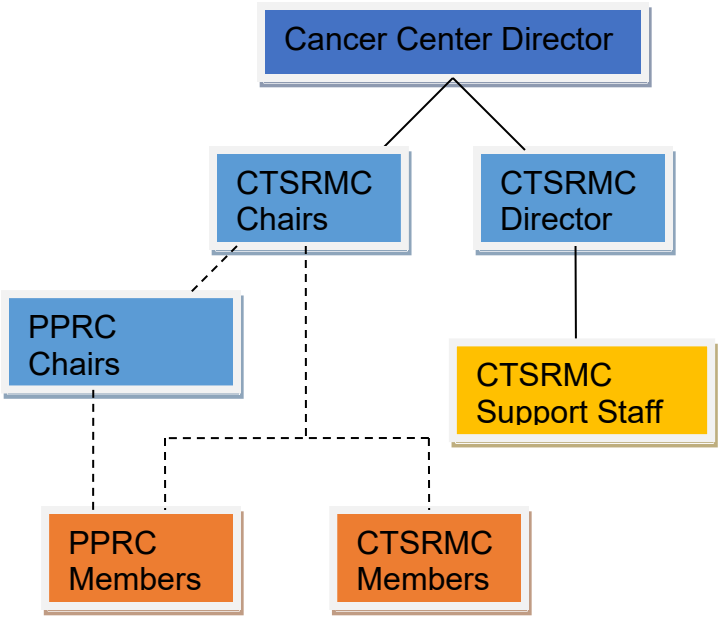
Ongoing CTSRMC approval (Post Initial Approval)

All protocols that have received CTSRMC approval via either expedited or full-committee review must send all amendments, modifications, clarifications and notifications to the CTSRMC/PPRC for review and approval before or at the same time that they are sent to the IRB. Submissions must not be delayed pending IRB approval since the IRB often awaits CTSRMC approval before making a final decision. For the fastest response, we strongly encourage study teams to submit documents via the CTSRMC common listserve CTSRMC_SUBMISSIONS@LISTS.UPENN.EDU. Study teams may experience delays if submission are provided directly through the IRB HSERA system due to IRB workflow rules.

All documents sent to the IRB to gain initial and ongoing approval must also be sent to the CTSRMC before or at the same time as they are sent to the IRB. These requirements (and others) are outlined in the initial CTSRMC approval letters.

Failure to comply with CTSRMC requirements may result in a study hold 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 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, 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 Tuesday of every month. This is a closed meeting. Therefore, PIs, Sub -Investigators and Study Coordinators attend only with special invitation. 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 polices. 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 eleven 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 Quality Control and 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 (AE/SAEs, MedWatch, etc.), evaluating protocol exceptions and deviations, assessing 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) resulting from unacceptable audit outcomes.

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, regulations 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 regard 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 reciprocate, 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.

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 for adult studies, and the pediatric CRQA assigns risk for the pediatric studies, which sets the stage for the compliance activities and oversight conducted by the DSMC and CRQA. The DSMC and CRQA committees function independently of the PRMC 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.ctsrmc.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 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** (*template can be found on website www.ctsrmc.org)* 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 PennCRMS (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 stepwise 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. Any changes to areas detailed above require an amendment to the MOP and documented ongoing DSMC approval of the MOP.

- **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, or insufficient 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, but not identical to 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 high-risk protocols that were reviewed by the CTSRMC via full committee are required to request exceptions from the DSMC.** Exception requests must be submitted to the DSMC via the compliance listserve DOCM_COMPLIANCE@LISTS.UPENN.EDU

- **For In-house or studies**: Only protocols that qualify as HIGH risk based on the ACC Risk table found on page 5 must request an exception from the DSMC prior to moving forward. 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 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 (not DSMB), approval must be obtained from the Medical Monitor prior to submitting an exception request to the DSMC.
- **For all other studies:** The PI has the option of requesting DSMC review for an independent decision, however, the DSMC will not provide an approval and will not prevent the PI from moving forward.

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 per applicable IRB policy. Deviation reports must be submitted to the DSMC via the compliance listserve DOCM_COMPLIANCE@LISTS.UPENN.EDU

- DSMC Submission Requirements:
- Studies that qualify as HIGH risk based on the ACC Risk table found on page 5.
- Studies in the ACC ProCAP or Enhanced Auditing programs.
- Any deviation that requires reporting to the FDA, OHRP or any other regulatory or federal governing body. Such deviations must be reviewed by the DSMC prior to external submission.
- Any deviation that was determined to negatively impact subject risk, safety or the overall study endpoints. Such deviations must be reviewed by the DSMC prior to IRB and external submission.

The deviation report must include a full description of the deviation, date it occurred, date it was identified, if there were delays in identify the deviation, an explanation for the delay, the PI's assessment of the impact of the deviation(s), 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 (not DSMB), documentation of Medical Monitor assessment and recommendations/required actions must be included with the submission to prevent delays in DSMC review.

- For deviations not included in mandatory reporting above, the PI has the option of requesting DSMC review for an independent decision, however, the DSMC will not mandate follow-up actions or reporting unless subjects were harmed or placed at increased risk. DSMC review will be limited to the scope specifically requested by the PI.

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, risk to subject and/or study endpoint integrity and must be signed by the PI. Deviations that do not include the PI's documented assessment are not acceptable. (*visit our website www.ctsrmc.org for details)*

Upon receipt of a deviation report, the DSMC (or at least a Chair and one member) will assess 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, enrollment and the level of external monitoring and/or auditing. See Department of Compliance and Monitoring (DOCM) Auditing Timelines section 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

Preliminary findings will be discussed with the study team during the audit close-out. The study team has five business days following the close-out to address any misunderstandings and/or provide promised documentation. The audit letter will be finalized at the end of the five-day period or sooner if the study team notifies the auditor that no further follow-up is necessary. Deficiencies identified in the audit letter will be evaluated by the DSMC Director and a final audit letter will be issued. The PI will be notified in writing of the audit findings and required corrective actions. Deficiencies will be identified as Minor, Moderate and Major using a hybrid of the CTEP CTMB guidelines. All audit responses must be signed by the PI and received by the date identified in the letter. Responses received without PI signature or documented authorization will not be accepted. A final evaluation of the level of the study deficiencies will be made after the response has been received. When possible, the DOCM uses the CTEP CTMB audit deficiency categories, however, for NCTN trials that are being conducted as part of an FDA marketing application and for non-NCTN trials, deficiency categories may vary based on known FDA expectations and/or prior FDA inspection feedback. The DOCM audit process and operations are not intended to mimic CTEP CTMB.

Lesser Deficiencies

A finding that does not have significant impact on the outcome or interpretation of the study and is not described as a major deficiency. An unacceptable frequency/quantity of lesser deficiencies (patterns) are assigned as a major deficiency when determining the **final** assessment of an audit component.

Corrective Actions

Upon notification of deficiencies, the PI will be given 30 business days o 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 may require a response to the audit letter. The findings will not warrant an off-schedule re-audit of the study.

Major Deficiencies

- A variance from protocol-specified procedures, or practices that make the resulting data questionable. If numerous impactful findings reveal a pattern of deficiencies in PI or Sponsor-Investigator oversight, they will be categorized as major which may, depending on the total number of findings, result in an unacceptable outcome.

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 the 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 until satisfactory corrective actions have been implemented and proven effective through auditing.

Corrective Actions

Upon notification of deficiencies, the PI and their 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). DOCM auditors will provide guidance and suggestions to the study team to help them during the corrective action process. An evaluation of the deficiencies will be conducted upon receipt of the PI's response and corresponding CAP. The findings will warrant a mandatory training session held by the DOCM and 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 Penn 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 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 permanent 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.

Critical Deficiencies

Any condition, practice, process, or pattern that adversely affect the rights, safety or well-being of the patient/study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data.

Corrective Actions

Upon notification of deficiencies, the PI and their staff are required to correct the deficiencies and develop a plan that will prevent such deficiencies in the future. The PI is given ten business days to respond to these findings, enrollment must be temporarily halted during the response period and development and implementation of a Corrective Action Plan (CAP) must be completed at the time the response is received. DOCM auditors will provide guidance and suggestions to the study team to help them during the corrective action process. An evaluation of the deficiencies will be conducted upon receipt of the PI's response and corresponding CAP. The findings will warrant a mandatory training session held by the DOCM and 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 Penn 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 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 permanent 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 **10 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 high-risk studies (includes subjects at other sites participating on 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 PennCRMS (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 monthly. 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 differ from the IRB because the goal of AE review is different. The DSMC requires submission of AEs as follows:

On-Site subjects (this includes any subjects enrolled at other sites on an ACC IIT or multi-site study). **Only events on studies categorized as HIGH risk based on the ACC Risk table found on page 5 must be submitted to the DSMC as follows:**

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 days of knowledge.
3. All other deaths within 30 business days of knowledge. Deaths of subjects greater than 90 days from last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

In-house studies receiving only funding/drug from a pharma/biotech company, government entity or other sources are not considered "sponsored".

Studies sponsored (full regulatory and operational responsibility) by the University of Pennsylvania, NCTN, other academic centers, government agencies, foundations, consortia, etc. do not qualify for DSMC reporting since those entities have the legal responsibility for evaluating risk and safety.

Study PIs have the option to request DSMC review of AEs that do not meet the high-risk definition if they would like an independent opinion of the event. The DSMC review will be limited to the scope specifically requested by the PI.

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. Each symptom is not required to be graded. The diagnosis represents the grade of the event. For events without a formal diagnosis, each symptom, which may be only an abnormal lab value, should be listed as an event.

The investigator 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 investigator 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 of previous information), then the report should be corrected promptly.

All AEs should include grade, attribution and expectedness as determined by a study investigator listed on the Delegation of Authority log Only an investigator may determine the diagnosis, attribution and expectedness and must also confirm that the details of any reports or logs prepared by a member of the study team are complete and accurate including grade.

- For attributions of "unrelated", an alternative explanation must be provided to explain to what the event is being attributed. Events submitted without an explanation will be queried by the DSMC.
- 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

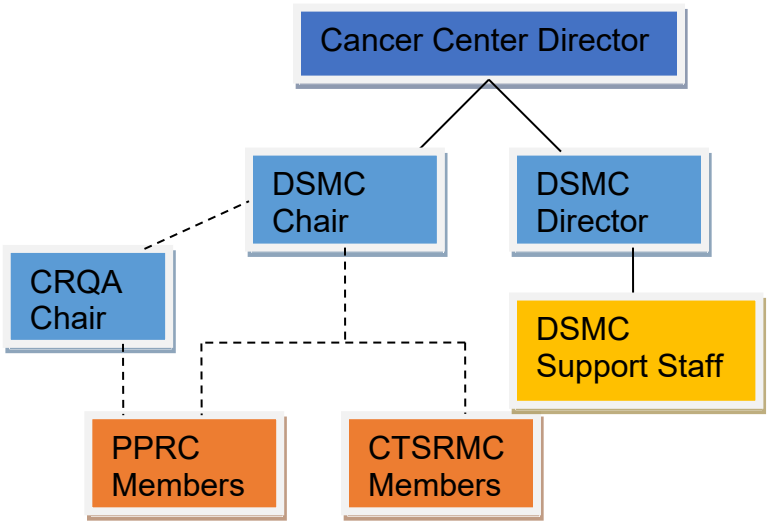
All events must be entered into the ACC Clinical Trials Management System (CRMS using the centralized reporting form. This form was developed by the DOCM and contains all of the elements required by regulatory agencies and the DSMC for appropriate tracking and management. Entry of data into the AE/SAE 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 CRMS or responses to queries should be sent via the listserve to DSMC_AE@LISTS.UPENN.EDU.

Updating/Correcting Reported AEs

Once an event is reported, you must keep the information accurate and current in Velos/CRMS. If new or updated information is learned about a previously reported event, a new Follow-Up report should be created. The initial report should not be deleted since these data may already be under review by the DSMC.

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 CRMS (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 assigned risk 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, data quality and research 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 CTSMRC 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.

- **Institutional/In-house-** Audited by the DOCM as required by the risk level detailed on the ACC Risk table on page 5.

- **Externally Peer Review Sponsored-** EPR studies can fall into two categories:
  1) Penn investigator initiated with funding from an EPR agency- Are considered In-house and are treated and audited as such.
  2) ACC investigator participating in an external EPR study (funding not held by PI)-
  Treated and audited like In-house unless the study has an independent oversight body that monitors/audits the study at least once a year. Copies of monitoring/audit letters must be submitted to the DOCM within 30 days of the monitoring visit/audit. Failure to provide letters may result in a study hold.

- **NCTN/NCI Cooperative Groups -** All NCTN studies that are part of the ACC portfolio are audited by the DOCM including network and affiliate sites. All sites must comply with DOCM requirements for quality and compliance. Failure to comply may result in a study hold at the site, or a hold on a site participating in any protocol conducted under the ACC.
  In addition to routine auditing, NCTN study PIs may request their study be part of the DOCM Enhanced Auditing or ProCAP oversight programs.

- **Pharmaceutical/Biotechnical Industry**- Because these sponsors have approved oversight programs, the DOCM does not audit these protocols unless there is a for-cause need or the PI requests their study be part of the DOCM Enhance Auditing or ProCAP programs.

Pediatric Trials- Pediatric trials are assigned audit schedules based on risk determinations made by the CRQA and subject to approval by the DOCM. At a minimum, audit schedules will follow ACC auditing timelines as per risk categories defined in the ACC Risk Table.

The FDA continues to update their guidance on risk-based monitoring of clinical research allowing for remote and hybrid oversight. The DOCM works closely with the ACC DSMC and study investigators to design the best risk-based auditing process based on the specific design and needs of the study. The most current FDA guideline, *A Risk-Based Approach to Monitoring of Clinical Investigations* is taken into consideration during the development of the DOCM risk-based approach model.

ICH GCP has addended their original guidelines to include the following:
Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original text. Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results.

DOCM Auditing

High Risk- Top priority for the ACC

- 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.
- For studies with two consecutive acceptable audits with minor outcomes, the audit window may be extended by 3 months.
    - If the outcome of a subsequent audit reveals moderate or major outcomes, the audit window will revert to the original timeframe.
- High enrolling or quick enrolling studies are audited more frequently as necessary.
- Investigators are notified approximately 5 weeks in advance of the selection of their protocol for review and cases are randomly selected.
    - Notification of a for-cause audit may be less than 10 business days.
    - Notifications of audits in preparation of external audits/inspections may be less than 10 business days.
- Three subjects or 10% of the total accrual, whichever is higher, are audited.
    - NOTE: All subjects will be reviewed in the event of a for-cause audit and/or in preparation of external audit preparations.
- A formal report is provided to the PI approximately 30 business days after the audit.
- The DSMC 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 and study team to discuss the findings of the audit and necessary corrective actions.

Moderate risk

- Not routinely audited; priority is given to high-risk protocols.

- May be selected for an audit at the request of the DSMC.
- May be randomly selected for auditing as part of a routine quality system review.
- Investigators are notified approximately 5 weeks 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 after the audit.

Low risk

- Audited on a for-cause basis at the request of the PI, DSMC or ACC Director.
- Notification of a for-cause audit may be less than 10 business days.
- All subjects will be reviewed in the event of a for-cause audit. A formal report is provided to the PI approximately 30 business days after the audit.

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

Electronic Source Documents and Study Records

The ACC strongly advocates for the development of electronic study records to facilitate remote auditing of our studies (local, external and affiliates), as well as external monitoring (i.e., pharma, NCTN) and inspections (i.e., FDA, Health Canada, EMA). All studies conducted at locations beyond the main campus of the University of Pennsylvania must have electronic study charts in order to participate in ACC clinical research. Further information about the ACC's goals for electronic study conduct and remote oversight can be found in the following:

A unique window of opportunity for practical reform of cancer clinical trials
Vogl DT, Sallée V, Hendricks MC, Redlinger Tabery C, Blair ML, Dahlmeier E, Meagher EA, Cohen RB, Vonderheide RH. A unique window of opportunity for practical reform of cancer clinical trials. Cancer. 2021 Aug 15;127(16):2855-2860. doi: 10.1002/cncr.33585. Epub 2021 Apr 13. PMID: 33849079.

AAMC- Five ways that clinical trials might change for good
https://www.aamc.org/news-insights/five-ways-clinical-trials-might-change-good

Electronic source documents make it easy for all members of the study team to quickly access records regardless of their physical location allowing investigators to make quicker decision related to eligibility, treatment modifications and adverse events, and provide a better regulated method of study document version control which is critical for consenting and re-consenting subjects. In addition to facilitating day-to-day study conduct, electronic study records prevent delays in scheduling visits, reduce travel and on-site burdens, allows internal auditors to do early preparatory review, and post-audit teams can easily share documents related to auditing/monitoring findings to address identified issues.

Audit Format

Investigators will be given four options for the audit format:

1. **Fully remote audit**- All regulatory files and most subject records must be available in electronic format and will be reviewed remotely. The majority of paper-based documents must be converted to electronic. This is ideal if there are few paper-based source documents (not available in any electronic source)
    a. Required format for all locations beyond the University of Pennsylvania and CHOP main campus.
2. **Hybrid audit**- All regulatory files must be fully electronic and subject records available in an electronic source (e.g., EPIC) will be reviewed remotely. All paper-based records will be reviewed on-site with a member of the study team. This is ideal if there are a significant number of paper-based source documents (not available in any electronic source), and the study team does not want to convert paper to electronic format.
    a. Not available for locations beyond the University of Pennsylvania and CHOP main campus.
3. **Limited remote audit**- All regulatory files must be fully electronic and will be reviewed remotely, and all paper-based (not available in any electronic source- this is rare) subject records will be reviewed on-site.
    a. Not available for locations beyond the University of Pennsylvania and CHOP main campus.
4. **Fully on-site audit**- All regulatory files and subject records are only available in paper format (this is *extremely rare*).
    a. Not available for locations beyond the University of Pennsylvania and CHOP main campus.

If the auditor is not given access to all necessary study documents and systems on the day of the audit, the missing information will be recorded as deficiencies.

Audit 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 criteria are documented
        - All exclusion criteria are documented
- Treatment administration and accountability

  - Source documents of orders, dispensation and administration. Administration records should contain start and stop times or overall time of administration (as needed for the study), date, dose, height and weight (if applicable to dose calculation), pre or post-treatment medication, special preparation like flushing lines of other activities that could create variances in start and stop times.
  - Agents that are dispensed in the clinic for subject self-administration must 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.
  -
- Data verification
  - Source documentation to Case Report Form (CRF) validation (where applicable)
- Overall organization of the study, PI oversight, appropriate delegation, appropriate training, and study related knowledge of staff
- Pharmacy records
  - Shipping, receiving, return and destruction
  - Accountability (received, ordered, dispensed, remaining)
  - Storage conditions and temperature logs (where applicable)
  - Special preparation or handling
  - Staff training
  - SOPs related to topics such as disaster recovery, expired agents, Certificate of Analysis
- Manufacturing (where applicable)

Audit Close-out

An audit close-out meeting is not required but is strongly encouraged. If the study team does not want a close-out meeting, they should notify the auditor in advance. The audit close-out gives the study team and the auditor the opportunity to resolve or clarify findings, and to discuss next steps. Study teams are given five days after the close-out to provide clarification or missing documents to the auditor. The auditor will note on the audit letter that the issue was resolved post close-out. Findings resolved post close-out are not reflected in the final audit outcome assessment but are noted for quality control and quality improvement purposes.

Multi-location and Multi-site Auditing

Penn and CHOP fully own multiple institutions that my participate in clinical research. A study that is active at multiple owned facilities is categorized as multi-location. Studies that are active at multiple locations other than those that are fully owned are categorized as multi-site.

DOCM auditors must audit all participating sites. All Penn-owned locations outside of the main University of Pennsylvania and CHOP campus and all external sites will be audited remotely and must fully cooperate with this process. Any site that does not comply with DOCM remote audits, will be promptly closed by the DSMC and may be blocked from future participation in ACC clinical research. The Sponsor-Investigator is responsible for ensuring every site understand the obligations and oversight process prior to site initiation.

External sites must provide access to all study records through any of the following options:

- Penn-owned and CHOP-owned locations: Direct connection to EMR for subject records, all other documents via a secure sharing system
- External sites: Direct connection to EMR for subject records, all other documents via a secure sharing system, **OR**
- All study records via a secure sharing system, **OR**
- All records stored on an encrypted, password protected memory stick; shipped to the ACC via traceable mailing method (i.e., USPS, FedEx, UPS, courier, etc.)

DOCM auditors will only travel to external sites for-cause at the discretion of the DOCM Director. The PI is responsible for all costs incurred by the DOCM audit staff related to travel and travel-related expenses.

The DOCM will develop a custom Multi-site Audit Plan for each study. This plan will be incorporated into the Multi-site MOP that must be submitted to the CTSRMC/PPRC for final protocol approval.

The DSMC may request a hold or stop of enrollment at any participating site for concerns related to the sponsor-investigator's ability to appropriately oversee the site or issues at the site that impact compliance, safety or data quality. **Investigators are bound by the approved MOP. All changes to the MOP must be approved by the DSMC prior to implementation of the changes.**

Quality Assurance and Systems

In addition to mandatory operations discussed above, the DOCM makes available to ACC investigators the following support. Please contact the DOCM Director for details.

- **Multi-site Compliance Support (MCS)**

To support Sponsor-Investigators by designing a custom auditing plan and study Manual of Procedures (MOP), assisting with training, consulting with the Sponsor-Investigator on CRMS set-up for external sites, AE/SAE review processes, eCRF development, site-initiation, audit readiness, and other activities as needed.

  - **Mandatory for all multi-site treatment trials with an IND/IDE)**

- **Prospective Compliance Assessments Program (ProCAP)**

The ProCAP program is available to all ACC investigators and is designed to help investigators create and maintain an audit-ready study from start-up to completion. Quality and compliance reviews and guidance continue for the life of the study. **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 declined, but still have access to EIS.

- The study investigator must complete, sign and date the ProCAP request form. (*visit our website www.ctsrmc.org for details)***.**
- The DOCM will assess the study for appropriateness for the ProCAP program and notify the investigator that the request has been accepted.
- Once accepted into the ProCAP 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 ProCAP program. Studies removed from ProCAP can only re-enter upon PI appeal to the DSMC. The appeal must be made within 30 days of PI notice that their study was removed from the program. Appeals later than 30 days will not be accepted.
- Assessments are not formal audits so issues identified during assessments will be relayed to the study team via e-mail within 7 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.
- **Enhanced Auditing** (*fee-based service, contact the DOCM Director for details*)
- Designed to supplement the responsibility the PI has for ongoing monitoring of their study and help create and maintain an audit ready study. Different from ProCAP, Enhanced Auditing provides a customized, more intense audit schedule, additional training and support.
    - **Mandatory** for all investigator-held IND/IDE studies that are not supported by PSOM OCR.
- Available for all NCI/CTEP sponsored, funded or supported studies..
- Available for all other single-site IITs.

DOCM Role in External Audits/Inspections

- **NCTN Cooperative Groups**
    - Because NCTN 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 play a large role in preparation and provide expert guidance as necessary.
    - Upon notification by an NCTN group, the NCTN Program Leader or Program Manager will notify the DOCM Director of the audit announcement at which time, the DOCM Director will initiate external audit preparation activities.
    - The DOCM will establish preparation standards, schedules, activities, and activity-related milestones to ensure the study documents are in a state of audit readiness in time for the group audit.
        -
    - Upon notification by the NCTN group of the protocol and subject case lists, the NCTN Program Leader or Program Manager will notify the DOCM Director who will initiate the next

phase of audit preparation targeting the studies and subjects identified on the case list released by the NCTN group.

- The NCTN Program Leader and Program Manager will coordinate and facilitate the group audit and provide a daily update to the DOCM Director.
    - The DOCM Director must be consulted for issues related to ACC operations, any regulatory, compliance or significant safety issues.
- The NCTN Program Leader, Program Manager and study PI will draft the site response to audit findings and provide to the DOCM Director for final review and approval.
- The DOCM Auditors will work with study teams post-audit to implement corrective actions required by the DSMC, CTEP or the cooperative group.

- **NCI/Theradex Audits**

Due to the risk to the entire ACC research program, and impact on the ACC NCI Core Grant, 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 ProCAP 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, thus the DOCM will fully manage the audit with a hybrid approach:
        - Following the close-out of the inspection, DOCM will work with the study team(s) 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.

- **Federal/Government Regulatory Agencies**

At the time an external audit/inspection (FDA, EMA, Health Canada, etc.) notification is received for any study the DOCM Director/ACC Chief Compliance Officer- Clinical Research must be immediately notified.

- 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 team as they prepare to guide them as needed.
- The study team will fully manage the day-to-day of the inspection with updates provided to the DOCM Director at the end of each day.
    - DOCM staff will be available to the study team during the inspection to answer questions and/or provide support.

- **The DOCM may take over management of the inspection at the discretion of the DOCM Director and/or DSMC Chair**Following the inspection close-out, 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.
- All responses to external inspections must be submitted to the DOCM Director/ ACC Chief Compliance Officer- Clinical Research for review and approval prior to submission of the response to the external regulatory agency.
    - Failure to comply with this requirement will result in a modified process for the study team/research unit going forward.

HIPAA

Every audit includes a basic 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.

Data Confidentiality

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 un-blinding.

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 ensure compliance with NCI requirements for Designated Comprehensive Cancer Center.

CTSRMC

- Study status updates to ANY study must be immediately applied in Penn CRMS (Velos).
    - The definitions for, and use of the various statuses can be found on our website www.ctsrmc.org
    - Study statuses and status dates must be updated as the status changes
- A copy of the IRB Continuing Review (as applicable to IRB policy) 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 must be submitted to the CTSRMC for review as part of scientific progress monitoring.
- All subjects must be registered in Penn CRMS (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.ctsrmc.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 studies and subjects. Please see our website www.ctsrmc.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 listserve DOCM_COMPLIANCE@LISTS.UPENN.EDU
- AEs and SAEs that meet the DSMC requirements for reporting must be entered in Penn CRMS (Velos) within 10 business days of occurrence. Unexpected deaths must be entered within 48 hours of study team awareness.
- DSMB and Medical Monitoring decisions related to study status or subject safety/protections must be sent to the DSMC within 48 hours of receipt by the study team.
- All correspondence from sponsors or regulatory agencies regarding safety or study design issues for protocols approved by the CTSRMC via the full-committee process.

Clincaltrials.gov (CTG)

The DOCM plays an active role in ensuring compliance with CTG registration, maintenance and outcomes reporting in compliance with Section 801 of the Food and Drug Administration Amendments Act known as FDAAA 801. Registration is required for studiesthat meet the definition of an "applicable clinical trial" (ACT) and either were initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007. ACTs, are defined in section 402(j) of the PHS Act.

In addition to FDAAA 801, The National Institutes of Health (NIH) Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by the NIH, will ensure that their NIH-funded clinical trials are registered at, and that summary results information is submitted to, CTG for public posting. The purpose of the policy is to promote broad and responsible dissemination of information from NIH-funded clinical trials through CTG. Disseminating this information supports the NIH mission to advance the translation of research results into knowledge,

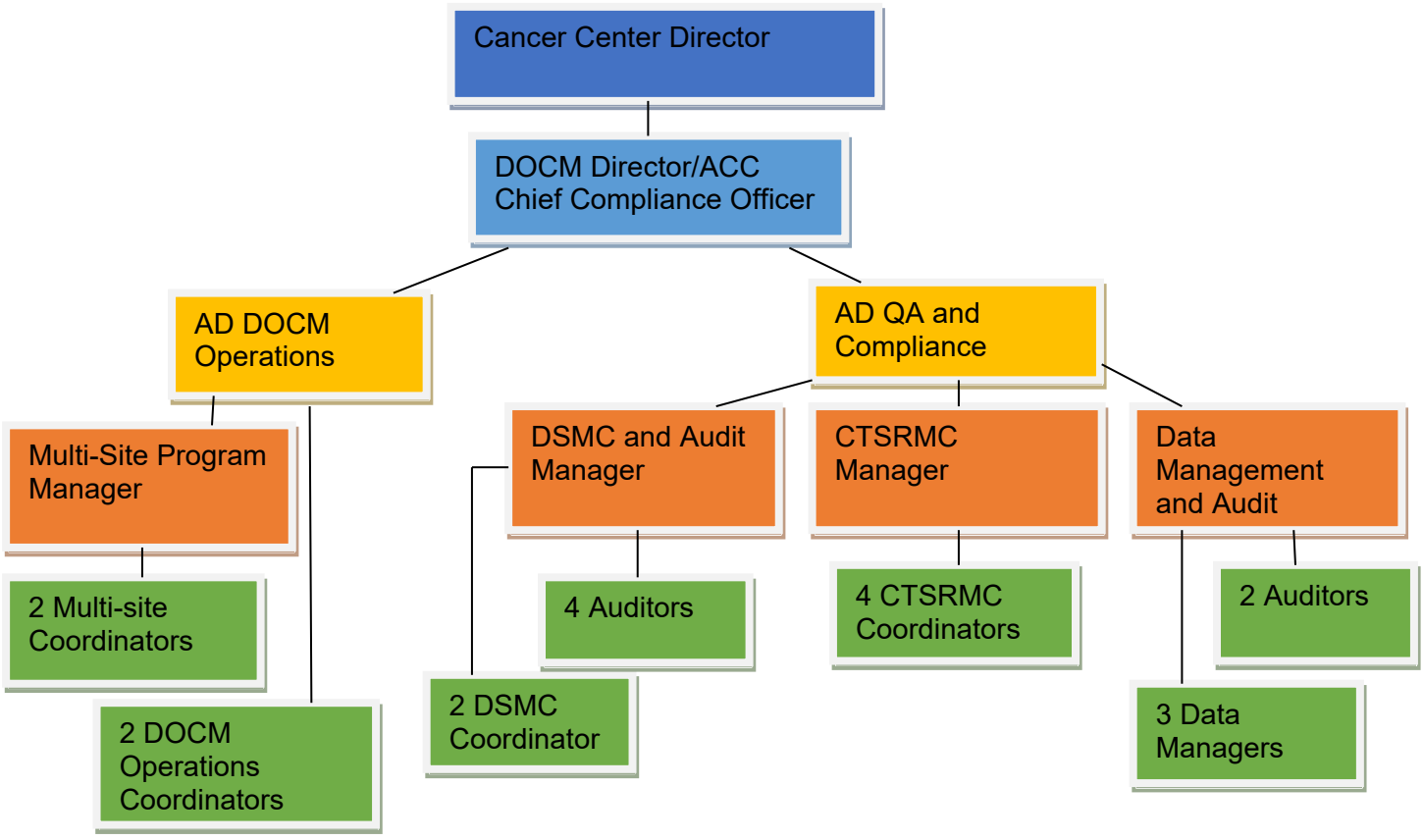
products, and procedures that improve human health. This policy is complementary to 42 CFR Part 11.

The ACC is also accountable to the NCI Clinical Trials Reporting Program (CTRP) for CTG registration. The NCI CTRP program closely monitors cancer center compliance with CTG registration and validates registration of protocols across both systems (CTRP and CTG). To prevent the ACC from falling into non-compliance, and to ensure complete, accurate and timely data are provided to the NCI per CCSG guidelines, the DOCM has designated coordinators to assist investigators with every aspect of CTG. The DOCM created an ACT determination checklist for studies that are not funded by the NIH and a separate checklist for those funded by the NIH to navigate investigators through the decision process. These checklists are sent to the investigator following CTSRMC approval (expedited or full). Investigators are required to complete the checklist and return it to the DOCM within 15 business day. The DOCM will help investigators navigate CTG registration, maintenance and outcomes reporting and will conduct periodic quality reviews of registered studies to ensure they align with information tracked by the DOCM related to amendments, enrollment status, study design updates, contact information and other key data elements. In order for DOCM coordinators to assist ACC investigators, all cancer-relevant protocols must be registered in CTG under the Abramson Cancer Center. Investigators with protocols out of compliance with CTG will be given 30 business days to become compliant before the DOCM initiates corrective actions. Section 801 of FDAAA authorizes civil monetary penalties against responsible parties who fail to comply with registration and/or results submission requirements. In addition, in relation to federally funded studies, section 402(j)(5)(A) of the PHS Act provides for the **withholding of remaining or future grant funds from a grantee** for failure to submit clinical trial registration and results information.

Per the FDA, the final rule outlines the potential civil or criminal actions, including civil monetary penalty actions, and grant funding actions that may be taken if responsible parties fail to comply with the rule's requirements. **It does not outline all potential legal consequences, e.g., laws governing the veracity of information submitted to the federal government, however, and should not be understood as describing the only types of enforcement that the government might undertake with respect to compliance** with the provisions of section 402(j) of the PHS Act, including its implementing regulations.

ATTENTION: Protocols may be placed on temporary hold, or permanently closed for failure to comply with CTG registration and maintenance since non-compliance violates federal regulations and jeopardized the ACC's core grant. Investigators who fail to comply with CTG registration or maintenance will be reported to the Penn Office of Audit, Compliance and Privacy, the Vice Provost for Research, their Department Chair and the ACC Director.

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, they 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 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 reviews 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

The ACC DOCM functions on behalf of, and in compliance with, the NCI and NIH requirements for Cancer Centers. The DOCM oversight extends to all University schools/centers/institutes, etc. that are involved with cancer-relevant research. The DOCM does not specifically function on behalf of the University, however, the University benefits from this additional oversight.

- **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 DOCM and PSOM OCR are separate oversight entities. The PSOM OCR functions on behalf of, and in compliance with, the PSOM and University guidance and policies. The ACC DOCM will work collaboratively with the OCR to help the PSOM accomplish common goals in so far as doing so does not impact ACC compliance with the NCI/NIH or violate this NCI approved ACC Institutional Data and Safety Monitoring Plan (IDSMP).
  - **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, 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 ACC accomplish common goals.

Technologies

Website (www.ctsrmc.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 collection and reporting needs of the CTSRMC, 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 continues to grow to enable dynamic data visualization and performance tracking.

PennCRMS (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 CRMS 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.

PennCRMS commonly known as 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.

Veeva SiteVault

SiteVault is the ACC's electronic Investigator Site Files (eISF) management tool. SiteVault provides an efficient way for investigators and study teams to maintain and access their regulatory and other study source documents electronically, allows for electronic signatures, digitizing delegation of authority/task lists and facilitates remote monitoring/auditing in accordance with ICH-GCP and federal regulations. **Administrative Information**NIH policy requires that grantees have in place procedures for Data and Safety Monitoring of clinical trials. This is to ensure 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.

Food and Drug Administration (FDA)

www.fda.gov

National Library of Medicine Clincaltrials.gov (CTG)

https://clinicaltrials.gov/policy/fdaaa-801-final-rule


the cure is within
ABRAMSON CANCER CENTER


Children's Hospital
of Philadelphia
Cancer Center