

**Data and Safety Monitoring Plan for Clinical Trials
Institutional Plan of the
Case Comprehensive Cancer Center**

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SUMMARY

This document describes the components and operating procedures that govern the data and safety monitoring of cancer clinical trials conducted at the Case Comprehensive Cancer Center (referred to throughout this document as Cancer Center or Case CCC). The Case CCC is a consortium that includes all cancer research at Case Western Reserve University (CWRU), University Hospitals Seidman Cancer Center (UH SCC), and Cleveland Clinic Taussig Cancer Institute (CC TCI). This policy applies to all clinical trials conducted under the aegis of the Case Comprehensive Cancer Center.

All clinical trial protocols have in place a Data and Safety Monitoring Plan (DSMP) approved by the Cancer Center Protocol Review and Monitoring Committee and local Institutional Review Boards, and aligned with this NCI-approved plan. This plan ensures the safety of participants, the validity of data, and the appropriate termination of studies in the event that undue risks have been uncovered, or when it appears that the trial cannot be completed successfully. The institutional plan covers all phases of interventional clinical trials. Particular attention is given to monitoring investigator-initiated clinical trials, especially those for which there is no independent extramural monitoring program. The responsibility for data and safety monitoring in the Cancer Center primarily rests with the Data Safety and Toxicity Committee (DSTC).

ACKNOWLEDGMENTS

The Case Comprehensive Cancer Center is greatly indebted to efforts of the National Institutes of Health, particularly the National Cancer Institute, whose data and safety monitoring policies and plans formed the basis of our data and safety monitoring plan.

ABBREVIATIONS

AdEERS	Adverse Event Expedited Reporting System
AE	Adverse Event
AER	Adverse Event Reporting
CAP	Corrective Action Plan
Case CCC	Case Comprehensive Cancer Center
CC	Cleveland Clinic
CCR	Center for Clinical Research
CCSG	Cancer Center Support Grant
CDUS	Clinical Data Update System
CR	Continuing Review
CRO	Clinical Research Office
C-ROC	Clinical Research Operations Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTC	Common Toxicity Criteria
CTEP	Clinical Trial Evaluation Program
CTRP	Clinical Trials Reporting Program
CTU	Clinical Trials Unit
CTWG	Clinical Trials Working Group
CWRU	Case Western Reserve University
DLT	Dose Limiting Toxicity
DSM	Data and Safety Monitoring
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
DSTC	Data Safety and Toxicity Committee
FDA	Food and Drug Administration
IDE	Investigational Drug Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
IIT	Investigator-Initiated Trial
MP	Monitoring Plan
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities
PI	Principal Investigator
PRMC	Protocol Review and Monitoring Committee
QA	Quality Assurance
SAE	Serious Adverse Event
SCC	Seidman Cancer Center
SOP	Standard Operating Procedure
TCI	Taussig Cancer Institute
UH	University Hospitals
UHCMC	University Hospitals Cleveland Medical Center

I. OPERATIONAL DEFINITIONS

The components of clinical trial development, review, conduct, operations, biostatistical assessment, quality assurance, audit reports, and consortium clinical trial oversight are described in the Cancer Center Clinical Trials Operations Manual available at the Case CCC web site at: <http://cancer.case.edu/research/clinical-research-office/>

To guide the reader of the Data and Safety Monitoring Plan (DSMP) the following operational definitions of the components of the Cancer Center clinical trials operations are provided.

I.1. Definition of Clinical Trials

The National Cancer Institute (NCI) defines a clinical trial operationally as “a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it.”

Definitions used here are from the P30 Cancer Center Support Grant Data Table Guide 2017. The DSMP of the Case CCC governs cancer clinical trials, i.e. interventional clinical research, defined as: individuals are assigned prospectively by an investigator based on a protocol to receive specific interventions. The participants may receive diagnostic, treatment, 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.

The primary purpose of an interventional trial may be:

- Diagnostic: protocol designed to assess one or more interventions aimed at identifying a disease or health condition.
- Prevention: protocol designed to assess one or more interventions aimed at preventing the development of a specific disease or health condition.
- Supportive Care: 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: protocol designed to evaluate one or more interventions for treating a disease, syndrome, or condition.

Observational studies and Ancillary or Correlative studies are not considered clinical trials. Patient risks associated with clinical trials are largely related to underlying characteristics, novelty and experience with the treatment intervention, the nature of the study population, and the ability to provide oversight of multicenter trials. The degree of monitoring is proportional to this risk.

I.1.1 Phase I Clinical Trials

Phase I trials are designed to test new therapeutics, often in a dose escalation manner, seeking evidence of maximum tolerated dose, dose limiting toxicity (DLT), safety of administration, and identification of novel toxicities.

I.1.2 Phase II Clinical Trials

Phase II trials are designed to test treatment regimens for efficacy in a limited number of diseases or molecularly-characterized populations and to provide evidence of tolerance and response. Early phase clinical trials of molecularly-targeted agents may blur the distinction between phase I and II, and new study designs may explore clinical activity in phase I studies.

I.1.3 Multicenter and Phase III Clinical Trials

A multicenter research trial is a clinical trial conducted at more than one medical center or clinic. Most large clinical trials, particularly Phase II and Phase III trials, are conducted at several clinical research centers. The benefits of multicenter trials include a larger number of participants, different geographic locations, the possibility of inclusion of a wider range of population groups, and the ability to compare results among centers, all of which increase the generalizability of the study. In many cases, efficacy will vary significantly between population groups with different genetic, environmental, and ethnic or cultural backgrounds ("demographic" factors); normally only geographically dispersed trials can properly evaluate this.

Phase III clinical trials are expanded controlled trials, typically conducted after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide adequate basis for drug licensing.

I.1.4 Stem Cell Therapy

Clinical trials involving immunosuppressive or high dose therapy followed by the infusion of autologous or allogeneic cells may give rise to life-threatening toxicities, including pulmonary toxicity, graft versus host disease, or debilitating opportunistic infections. While many of these studies have curative intent, morbidity and mortality may be high.

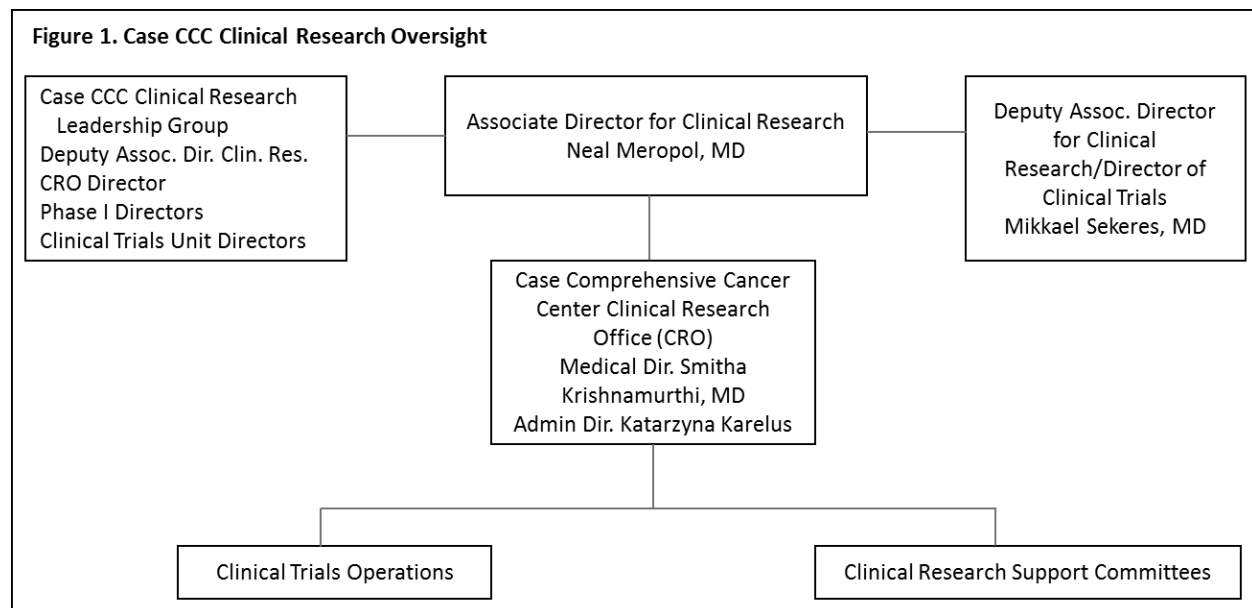
I.1.5 Gene Transfer Studies

Gene Transfer or gene therapy clinical trials represent novel, new therapeutics given to small numbers of patients. These trials attempt to treat disease by gene transfer. The immediate and long-term risk of these studies is often unknown. These trials are categorized as recombinant or synthetic nucleic acid molecule research.

II. DESCRIPTION OF OFFICES AND COMMITTEES INVOLVED WITH DATA AND SAFETY MONITORING

II.1 Clinical Research Office

The Clinical Research Office (CRO) oversees and coordinates all clinical research administration components relevant to the conduct of clinical trials across our consortium, including the committees that ensure quality and access (Figure 1). The CRO is led by a Medical Director and Administrative Director. The CRO reports through the Associate Director for Clinical Research, to the Center Director. The Deputy Associate Director for Clinical Research/Director of Clinical Trials has oversight of our Clinical Research Operations Committee (C-ROC), and provides leadership and advocacy for clinical trials research at CC. The leaders, plus the medical directors of the phase I programs and clinical trials units (CTUs) at each clinical site comprise the Clinical Research Leadership Group that is responsible for all operational and scientific issues related to clinical research across the consortium.



As a consortium cancer center, the CRO coordinates operations at the affiliated medical centers. Clinical Trials Operations oversight includes:

1. CTU at CC and UH which are responsible for the development, conduct, and management of specific clinical trials
2. Clinical trials registration (i.e. CTRP, Clinicaltrials.gov)
3. Quality assurance
4. OnCore[®] Clinical Trials Management System
5. Training and education of investigators and staff

The Clinical Research Support Committees overseen by the CRO include:

1. Protocol Review and Monitoring Committee (PRMC)
2. Data Safety and Toxicity Committee (DSTC)

3. Clinical Research Operations Committee (C-ROC) and Clinical Trials Working Group (CTWG)
4. Minority Accrual to Clinical Trials Committee (MAC)

The CRO provides support for all cancer clinical trials, from protocol development through reporting of results. The Office also oversees use of the OnCore® clinical trials database, ensuring timely maintenance of protocol status and patient accrual.

II.2 Clinical Trials Units

The Clinical Research Office oversees the Clinical Trials Units (CTUs) at University Hospitals SCC and Cleveland Clinic TCI, which provide an infrastructure (e.g. research nursing, data management, regulatory, quality assurance and financial aspects) to support investigators conducting cancer clinical trials. With its in-depth expertise in coordinating, managing and monitoring different types of studies including complex early phase and investigator-initiated trials, the CTUs play a crucial role in this important research area. The CTUs within the CRO are responsible for providing oversight, performance monitoring and training of their staff. Additional education and training e.g. with OnCore® Clinical Trials Management System are provided by the CRO.

Any clinical trial conducted outside of CTUs has specific institutional oversight. At UH, clinical research staff outside of the CTU receive training and Quality Assurance (QA) oversight from the UH Clinical Research Center. At the Cleveland Clinic, clinical research staff outside of the CTU receive OnCore® training through the TCI CTU. Other training and QA oversight is done either by Center for Clinical Research (CCR) or by the respective institute's research administrator/program manager as applicable under the direction of the QA program from Research Compliance.

Both CTUs in the CRO work together on synchronizing and centralizing many of the clinical trials-related activities, policies and Standard Operating Procedures (SOPs). Both CTUs utilize the same database (OnCore®) for patient and trial-related information. All cancer clinical trials, whether supported by CTUs or not, are required to use the OnCore® database.

Research nurses monitor all patients on clinical treatment protocols covered by the DSMP. Patients are evaluated during treatment and at protocol specified follow-up visits. Toxicities that occur on phase I or stem cell trials are assessed and reported to their respective committees each week. Serious adverse events (SAEs) are reported to the attending physician, the principal investigator (PI), the DSTC, the respective Institutional Review Board (IRB), sponsor and to the appropriate agency. The CTU QA staff performs quality assessments to ensure accurate and timely collection and reporting of data, as well as compliance with all applicable regulations.

The CTU functions, as related to Cancer Center Support Grant (CCSG)-mandated functions and to NCI guidelines, are overseen centrally by the Case CCC CRO Medical Director and

Case CCC CRO Administrative Director, who provide coordination and oversight of the CTUs to ensure alignment of procedures and compliance with Cancer CCC policies.

II.3 Committees

II.3.1 Clinical Research Operations Committee

The Clinical Research Operations Committee (C-ROC) is the Case CCC policy and oversight committee which provides a regular forum for setting policies and procedures, and, discussing and resolving system-wide issues related to the conduct and support of clinical trials within Case CCC. The C-ROC plays a central role in setting clinical research policies and procedures and in communicating these to Case CCC leadership and research community at participating institutions. New and revised policies and procedures which are generally developed by the Clinical Trials Working Group, a C-ROC sub-committee and comprised of members from each consortium site, are distributed to C-ROC members for additional comments, review and approval by the C-ROC. All policies and procedures approved by C-ROC must receive final approval by the Cancer CCC Director before implementation. The Committee also discusses issues related to implementing and overseeing these policies and procedures at all institutions.

C-ROC meets monthly. There is no set quorum for the C-ROC meetings and it is up to the Chair to decide whether the number and/or composition of members at a given meeting is sufficient and appropriate for the discussion of a specific issue. Agendas are prepared for each meeting and formal meeting minutes are kept for record purposes and to document the Committee's decisions and plan of action. The minutes from meetings are considered peer-reviewed.

The Case CCC Director appoints all C-ROC members, including the C-ROC Chair, who is the Deputy Associate Director for Clinical Research/Director for Clinical Trials. Members are appointed for 3 years, and may be reappointed. Members include: Case CCC Director; Case CCC Administrative Director; Case CCC Associate Director for Clinical Research; Case CCC Deputy Associate Director for Clinical Research/Director for Clinical Trials; Case CCC Deputy Associate Director for Clinical Research/Director for Translational Research; Case CCC CRO Director and Medical Director; PRMC and DSTC Chairs; representatives from the Biostatistics & Bioinformatics Shared Resource; Directors and management from respective CTUs; faculty leaders in clinical trials and administrative representatives from the Case CCC institutions.

C-ROC's membership reflects the Case CCC inter-institutional composition. Through participation in C-ROC, institutional representatives are kept apprised of clinical trials policy issues and participate in their development. The C-ROC Chair is responsible for determining the best process for communication and follow-up regarding matters identified and discussed at the meetings. This is done in consultation with the Case CCC Director and Case CCC Associate Director for Clinical Research.

II.3.2 Clinical Trials Working Group

The Clinical Trials Working Group (CTWG) was initiated in 2009. Its meetings are coordinated by the CRO to facilitate communication across the consortium CTUs. The CTWG consists of CRO members including the Medical Director of the CRO; CTU Administrative and Medical Directors, CTU management e.g. in Regulatory, Quality Assurance, Data, and Nursing. The CTWG meeting provides a forum for discussing updates within the CRO and each CTU, reviewing clinical trials operations and areas in need of improvement. Standardized operating procedures (SOPs) are discussed and created by the CTWG with specific attention to investigator-initiated trials. This group authors SOPs and policies related to maintaining consistency and high quality for the conduct of the Case CCC clinical trials, which are then taken to the C-ROC for review and approval. The CTWG requires approval of the C-ROC for all new SOPs and policies. The SOP Manual is available on the Case CCC website at: <http://cancer.case.edu/research/clinical-research-office/>.

II.3.3 Protocol Review and Monitoring Committee

The Case CCC Protocol Review and Monitoring Committee (PRMC) is for a key component of the Case Comprehensive Cancer Center's Protocol Review and Monitoring System. In concordance with CCSG guidelines, the PRMC plays a critical role in protocol review and monitoring to assure that clinical trials are scientifically sound and that approved studies maintain adequate patient accrual and scientific progress.

Member nominations are solicited by the Center Director from the Associate Director for Clinical Research, Deputy Associate Director for Clinical Research, Medical Director of the CRO, Department chairs and Cancer Center Leadership. Appointments are made by the Center Director to ensure broad discipline representation. The co-Chair serves as chair-elect. At all times the Chair and Co-chair are from different institutions.

The PRMC members are nominated and selected to ensure diverse expertise relevant to cancer clinical research. The core membership is composed of pharmacists, nurses, senior and junior clinical investigators, biostatisticians, translational scientists and patient advocates. The membership represents the following areas: adult hematology and oncology; radiation oncology; dermatology; epidemiology and biostatistics; quantitative health sciences; behavioral sciences; nursing; cancer biology and drug development; investigational drug services; and CRO administration. Membership incorporates representation from each consortium institution. If specialized expertise for scientific review of a protocol is not adequate on the standing committee, ad hoc reviews are solicited. PRMC membership and functions do not overlap with the Data Safety and Toxicity Committee (DSTC). The CRO Medical Director does not chair, co-chair or serve on the PRMC or DSTC. The PRMC roster is shown in **Appendix E** and the DSTC roster is shown in **Appendix F**.

The PRMC meets twice monthly and reviews (as well as provides associated feedback to assist in protocol development) all new cancer-related clinical trials, conducted at the institutions

affiliated with the Case CCC, including investigator-initiated studies, protocols sponsored by the National Clinical Trials Network (NCTN), and the pharmaceutical industry. PRMC also reviews observational studies, except chart reviews, and ancillary and correlative studies, as well as major protocol amendments. CTEP-approved, NCTN trials, other previously peer-reviewed studies, studies reviewed by a scientific review committee from another NCI-designated cancer center, database and other studies, as determined by chair, undergo an administrative review by the PRMC Chair and/or Co-Chair without the need for full PRMC review. Protocols involving only retrospective chart reviews do not require review by the PRMC and proceed directly to the respective institutional IRB.

Any PRMC member with an actual or potential conflict of interest must recuse himself/herself from voting on a protocol with which he/she has a conflict. The PRMC minutes are uploaded to the PRMC website and anyone who wishes to review them is given access including the Case Cancer IRB staff and/or members.

PRMC primary functions are to:

- Foster the development of Case CCC research protocols which address the prevention, diagnosis, and treatment of cancer.
- Advise the Case CCC Director and respective IRBs on the scientific merit of proposed protocols.
- Provide protocol templates for all Case CCC protocols.
- Evaluate protocols for scientific merit and administrative completeness.
- Ensure that the data to be collected are appropriate for the study's goals.
- Review protocol-specific Data and Safety Monitoring Plans (DSMPs).
- Establish priority ranking for protocols within a given disease category.
- Perform full or administrative review of applicable amendments.
- Provide system-wide notification on changes in the study status (i.e. activations, suspensions, closures, terminations).
- Monitor the progress and patient accrual of Case CCC protocols.
- Mandate protocol closure as per policies described in the *Case CCC Clinical Trials Operation Manual* and *PRMC Accrual Review SOP (Appendix B)*.
- Review and follow-up, as applicable, on reports from the DSTC.

Protocol Prioritization

All trial protocols are prioritized by Disease Teams and subsequently by the PRMC at convened meetings. The PRMC assigns a priority score (total added score may vary from 5-18) (investigator-initiated trials are highest priority) for the protocol based on several criteria such as academic merit, feasibility and institutional participation. Priority scores are utilized in focusing on high-priority science, assuring adequate and appropriate patient population for each trial, evaluating competing trials, accrual monitoring, and allocating resources.

Accrual Review

The PRMC monitors accrual for: sponsored studies (industry, NCTN trials, institutional studies outside of the Case CCC); investigator-initiated studies; and rare disease studies. For studies conducted jointly at SCC and TCI, overall accrual is reviewed and both sites are informed about the study not meeting its accrual target even if the target is not met only at one site. Accrual analysis is conducted by PRMC utilizing OnCore® for patient enrollment information. Accrual review allows the Case CCC to monitor study progress and to evaluate and allocate trial resources in a timely fashion.

II.3.4 Institutional Review Board

Case CCC clinical trials are overseen by the Institutional Review Boards (IRBs) at consortium sites, i.e. University Hospitals Cleveland Medical Center and Cleveland Clinic. Both Institutions operate under their respective Federal-Wide Assurances and their IRBs are registered with the Office for Human Research Protections. Moreover, Human Subject Protection Programs at both IRBs are accredited with the Association for the Accreditation of Human Research Protection Programs, Inc.

It remains a high priority of the Case CCC to foster cancer-related clinical research collaborations between UHCMC and CC. To that end, the IRBs of each hospital have agreed to accept the approval of the other site in a facilitated review arrangement for cancer-related clinical trials. Thus, opening of cancer-related clinical trials at both sites requires only a single full board review at the site of the lead investigator.

A research study that does not involve cancer patients, e.g. an interventional clinical trial that is a prevention study or a non-interventional study such as an observational study, may be submitted to the Case Western Reserve University (CWRU) IRB.

IRBs adhere to federal, state and local regulations and guidelines for Human Subjects Research Protection and ensure that research meets ethical standards as per these regulations. The IRBs require certification of the PI and anyone who obtains written consent for the protocol in the area of human subject protection. This requirement also applies to CTU staff. The initial review of a cancer-related trial by the IRB can only take place after PRMC review and approval. As per IRB policies and procedures, the IRBs review protocols, consent forms, amendments, continuing reviews, SAEs and IND safety reports, protocol violations and deviations, and other study-related actions, as appropriate. As part of the continuing review process, the IRBs review study progress including accrual. IRB members are expected to objectively evaluate all protocols presented to the IRB to ensure adequate protection of human subjects. Any member with an actual or perceived conflict of interest must excuse himself/herself from voting on a protocol with which he/she has a conflict. All IRB members are required to complete a core educational program, a new member orientation and educational programs, as well as continuing education and training, as appropriate.

II.3.5 PRMC Relationship with IRBs

Once a protocol has been reviewed and approved by the PRMC, it is submitted along with the PRMC approval notice and scientific summary statement to the IRB office of the institution of the lead (e.g. UH or CC) principal investigator (PI). The study status is updated in OnCore® on an on-going basis to facilitate tracking by PRMC, PIs and regulatory coordinators. IRB submissions, reviews and approvals are monitored by the PI and regulatory coordinators. The consortium institutions have instituted an agreement that facilitates reciprocal approval by the secondary site's IRB to streamline activation of studies across the consortium.

II.3.6 Data Safety and Toxicity Committee

The Case CCC Data Safety and Toxicity Committee (DSTC) is the focal point in the Cancer Center for data and safety monitoring and the central body to review: 1) all internal SAEs and SAEs on investigator-initiated trials led by Case investigators including affiliated institutions; 2) all NCI-generated action letters; 3) IRB continuing reviews including review of toxicity for all interventional treatment investigator-initiated trials; 4) audit reports; 5) confirmation of objective responses reported in investigator-initiated studies; and 6) early stopping rule milestones as appropriate for the degree of risk in the particular clinical trial.

II.3.7 Review and Monitoring Committees for High Risk Clinical Trials

The primary considerations when determining the appropriate level of review and monitoring are the potential risks to study participants and the complexity of the trial. All active patients on high risk clinical trials (i.e. Phase I, stem cell therapy) are reviewed for intervention tolerance, toxicity, SAE reports, eligibility potential, completeness of data collection, and protocol violations by review and monitoring committees for high risk clinical trials. These committees are composed of PIs, treating physicians, research nurses, data managers, regulatory coordinators, pharmacists, and statisticians involved in patient accrual and management. Pertinent findings are reported to the DSTC. SAEs are independently reported to appropriate agencies (e.g. IRB, NCI/CTEP, NCTN, and industry sponsor) as outlined in this DSMP.

Agendas are prepared for each meeting and meeting minutes are maintained to document patient and study progress and/or status. When necessary, the CTU Quality Assurance (QA) teams at the respective institution assess first patient entry into high-risk investigator-initiated trials, including agents that are used first-time in humans.

II.3.7.1 Phase I Review Committee

At both the UH SCC and CC TCI, the Committee meets weekly and is led by a physician Chair. The team includes investigators; treating physicians; research nurses; data managers; pharmacist and regulatory and administrative staff. The Phase I Committee reviews the status of each enrolled patient on Phase I trials and evaluates laboratory and clinical data regarding toxicity, response, if applicable, and drug tolerance (dose finding). The team also reviews and discusses the number of open spots at each dose level. The regulatory staff provides regulatory updates on Phase I trials which are currently undergoing the PRMC and/or IRB

review and approval process. They also present information and approximate timelines when specific studies may be activated and open to enrollment. For joint UH-CCF studies, updates about enrolled patients are shared at the meeting.

Disease specific Phase I studies may also be managed and discussed within a given Disease Oriented Group at TCI.

Disease-agnostic genomic clinical trials are overseen by the Phase I Committees.

II.3.7.2 Stem Cell Therapy Trials

Each consortium hospital has a committee that reviews patients enrolled on stem cell therapy trials: the Hematopoietic and Immune Cell Biology meeting at SCC and the BMT Eligibility Meeting at TCI. Meetings are attended by investigators, treating physicians, nursing, and research staff. All patients enrolled on stem cell therapy trials and CAR T-cell trials are reviewed at these meetings for toxicity and outcomes.

11.3.7.3 Institutional Biosafety Committee

Institutional Biosafety Committees for CWRU/UHSCC and for Cleveland Clinic review recombinant and synthetic nucleic acid molecule research for compliance with the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. The Institutional Biosafety Committees meet monthly and meetings are open to the public. All new research, requests for continuing review, and significant protocol modifications are reviewed by the full committee. More information is available at <https://case.edu/research/faculty-staff/compliance/ibc/> and at <http://my.clevelandclinic.org/departments/clinical-transformation/depts/quality-patient-safety/biosafety-committee>.

III. ESSENTIAL ELEMENTS OF THE DSMP AT THE CASE COMPREHENSIVE CANCER CENTER

III.1 Monitoring the Progress of Trials and Safety of Participants

Clinical Trials Unit staff monitor all patients on Phase I through Phase III treatment clinical trials and present all toxicities to the treating physician for assignment of attribution. All toxicities are brought to the attention of the physician immediately and all expected toxicities are discussed prior to the start of each cycle-or anytime an intervention is warranted. Patients enrolled on phase I studies and stem cell therapy studies are monitored for toxicities and outcomes at their respective team meetings. Study nurses and/or research coordinators also assess patients on other interventional clinical trials.

Research nurses evaluate patients as appropriate for the particular clinical trial. The intensity of monitoring for toxicity is adjusted to the risk presented by the treatment intervention (greater risk in Phase I (dose-finding) and cell and gene therapy (dose-intense) trials than in Phase II and

NCTN Phase III trials. The assignment of risk level and associated degree of the monitoring plan is related with the interventional and institutional risk. All studies in which a Case CCC investigator holds the IND/IDE, Case CCC manufactures the study agent, or Case CCC-led multicenter trials are considered high risk. The PI of an IND/IDE and in selected instances for other investigator-initiated trial, with a designated monitor, prepares a monitoring plan based on risk. The plan includes frequency, scope, verification of data and verification of protocol compliance.

III.2 Compliance with Requirements for Adverse Event Reporting

All protocols are required to have a protocol section describing AE reporting. The PI must report all significant SAEs for drugs, biologics or devices to the IRB, to the protocol sponsor and, when applicable, the Food and Drug Administration (FDA) and National Institutes of Health (NIH) Office of Biotechnology Activities (NIH/OBA). The treating physician (co-investigator) is responsible for notifying the PI and research staff of the SAE. Appropriate forms and copies of all reports must be submitted to the IRB and DSTC.

III.2.1 IRB Review and Reporting Requirements

The consortium hospital IRBs, as well as the CWRU IRB, review all research involving human subjects and have the authority to approve, require modifications in, or disapprove all research activities, including proposed changes in previously approved human subject research. No human subject research that has not been approved by the IRB may take place at the Case CCC.

Following study activation, the consortium institution IRBs have the authority to observe and/or monitor Case CCC research to the extent they consider necessary to protect human subjects. The IRBs also have the authority to suspend or terminate research for serious or continuing non-compliance with the Common Rule, DHHS regulations, FDA regulations, or its own findings and requirements.

Each consortium institution IRB has a policy on reporting of AEs and unanticipated problems to ensure that the review, reporting and analysis of AEs and unanticipated problems occur in a timely, meaningful way so that human subjects can be protected from avoidable harms (see Appendix A(1), A(2), and A(3)). The policies outline procedures to ensure prompt reporting of AEs and unanticipated problems involving risks to participants or others to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency heads. These policies also include procedures for the PI and the IRB with regard to reporting and review of AEs and unanticipated problems.

The primary responsibility for the evaluation of reportability to the IRB lies with the PI of the trial. This includes the documentation, investigation, and follow-up of events. The mechanism and required time-frame of reporting to the IRB varies depending on the type of research study, significance, attribution, and expectedness of the event, whether it occurred internally or

externally, and if it is an AE that is also an unanticipated problem. Definitions and details of reporting requirements and procedures of respective institutional IRBs are provided in the **Appendix A (1), A(2), A(3) and A(4)**. At the completion of its review, the IRB is authorized to take any action needed to ensure subject safety, and protocol compliance. The IRB's decision is binding on all participating institutions.

III.2.2 Review of Toxicity Reports

SAEs that occur in patients on all types of interventional trials are recorded by the research nurse and/or coordinator and reviewed with the attending physician and the PI. Subsequently, the information on SAEs on high risk clinical trials, e.g. phase I and stem cell therapy, is presented and discussed at meetings of appropriate monitoring committees for high risk clinical trials. The investigators and the specific committees are responsible for monitoring the status of patients on active protocols under their jurisdiction. If a safety issue arises during these committee reviews, this too will be reported to the DSTC. The treating physician will assist research nurses in preparation of the SAE report and will sign the report. The SAE is submitted to the DSTC for review, and to the IRB, and is included in the official research shadow chart for each patient as well as the protocol regulatory binder in the CTU.

The DSTC review determines whether the SAE requires action such as a request for more information on the SAE, a recommendation to the PI to stop the dose escalation of a trial if a dose limiting toxicity (DLT) endpoint is reached, to hold accrual to the trial if an early stopping rule endpoint is reached, or to recommend closing a trial based on excessive toxicity. Toxicity grading criteria follow the most recently approved NCI Common Terminology Criteria for Adverse Events, unless the protocol specifies otherwise. It is the intent of the DSTC to provide oversight for the timely reporting of all internal serious reportable adverse events that occur to patients treated on interventional protocols to the IRB per each institutional reporting criteria, other reporting agencies and sponsors as dictated by the particular protocol, including the FDA, NIH, NCI/CTEP, NIH/OBA, and Institutional Biosafety Committee (for recombinant and synthetic nucleic acid molecule research).

The DSTC also reviews all external IND action letters.

III.3 Data Safety and Toxicity Committee

The purpose of the Data Safety and Toxicity Committee (DSTC) is to oversee all aspects of data monitoring and safety for interventional trials that are institutionally sponsored, investigator-initiated, and those trials that do not have external monitoring that are active at the Case CCC, and to provide oversight of patient safety for all other interventional trials (i.e. industry sponsored).. Non-interventional studies are considered low risk and oversight of data monitoring and safety are the responsibility of the Principal Investigator. The DSTC is an independent committee which does not duplicate either PRMC or IRB functions.

III.3.1 Committee Charge and Responsibilities

The charge of the committee is to: 1) oversee all aspects of data and safety monitoring for institutionally sponsored trials, investigator-initiated trials and, in particular, those trials that do not have external monitoring, such as those supported by NCI through R01, R21, P01, and U01 mechanisms that do not have Theradex or other external monitoring; and 2) provide oversight for patient safety for all other trials (i.e. industry-sponsored).

The Committee is responsible for the following functions:

- Review of all internal SAEs (regardless of study sponsor) and also review of external action letters and/or SAEs that are under investigator-initiated trials under DSTC purview.
- Review of IRB continuing review reports for investigator-initiated treatment trials. The DSTC receives continuing review reports specifically to review safety and compliance with applicable regulations and requirements. The DSTC determines whether an early stopping toxicity endpoint has been met and whether protocol and consent form modifications are needed. The DSTC reviews the IRB continuing review reports of clinical activity and outcomes for all institutional treatment trials that are open to accrual or for those trials that have been open and subsequently closed to accrual within the timeframe (one year) covered and reported on a given continuing review. These studies have had an activity of accrual (when they were open) and/or SAEs, and the DSTC focuses specifically on review of toxicity, response and safety. There is reconciliation of SAE reports submitted to the IRB and the DSTC. Clinical responses should only be reported in the continuing report if they have been confirmed by the DSTC. It is preferable that submission to the DSTC occurs prior to IRB submission.
- Review of major protocol violations; for example, ineligibility, consent form issues, treatment error or a treatment that is not within the guidelines of the protocol are reviewed in “real-time”. All deviations are reviewed by the QA teams at each institution in “real-time”, and those deemed to be minor deviations are submitted to the IRB at continuing review and are reviewed by DSTC at the annual review presented preferably prior to IRB submission.
- Review of audit reports. All audit reports are sent to the DSTC. When audit reports require corrective action plans, the plans are reviewed, and the DSTC determines if the proposal includes measures that adequately offer education or measures that correct the deficiency and prevent future errors.
- Request, as appropriate, changes in the consent form to inform patients of previously unrecognized risks, changes in dose modifications, schedules or toxicity monitoring.
- Review of any safety concerns and issues referred by either PRMC or monitoring committees for high risk clinical trials.
- Review all submitted protocol specific special safety reviews for selected institutional Phase I and II trials. Examples of these include novel agents, gene therapy, and trials of high complexity.
- Confirm independent review of all partial and complete responses of the Case CCC investigator-initiated treatment trials based on the criteria for response defined in the

protocol. Responses must be confirmed by independent review and submitted to DSTC to be considered reportable.

In the case that the Case CCC DSTC is the designated institutional monitoring body for a specific protocol, the DSTC will become the core review body for toxicity and data integrity for this trial. The DSTC, therefore, will review Outside Safety Reports, safety reports requiring action, adverse events and audit reports, as applicable, and may also review QA monitoring reports, if significant findings affecting either patient safety or data integrity are discovered.

III.3.2 Communication of Actions

The DSTC is an independent committee that communicates its decisions, such as immediate protocol suspension, recommendation of stopping of accrual, or recommendation of study termination to the PI, IRB, PRMC, CRO Medical Director and to the Associate Director for Clinical Research. The DSTC has authority to immediately suspend a protocol. DSTC recommendations to close a trial to accrual or terminate a trial, however, are forwarded to the IRB, which has the authority to implement these actions. It is the PI responsibility (with support of the CTU or CRO) to communicate the DSTC actions to the study sponsor and other oversight agencies, as applicable and/or as dictated by a particular protocol. In addition, the DSTC sends the meeting minutes to the PRMC, CTU Medical Directors, CRO Medical Director and Administrative Director, and Associate Director for Clinical Research.

III.3.3 Membership and Meetings

Member nominations are solicited by the Center Director from the Associate Director for Clinical Research, Deputy Associate Director for Clinical Research, Medical Director of the CRO, Department chairs and Cancer Center Leadership. Appointments are made by the Center Director to ensure broad discipline representation. The co-Chair serves as chair-elect. At all times the Chair and Co-chair are from different consortium institutions.

Membership is for a renewable term of 3 years. The membership allows adequate review of protocols and includes members with diversified expertise from the following areas: medical oncology radiation oncology, nursing, investigational drug services, epidemiology & biostatistics and quality assurance.

Membership incorporates representation from each consortium institution. DSTC membership has no overlap with the PRMC membership. The CRO Medical Director does not chair, co-chair or serve on either DSTC or PRMC. The DSTC roster is shown in **Appendix F** and the PRMC roster is shown in **Appendix E**. All Case CCC investigators, DSTC members, PRMC members and CPDM staff are trained in Health Insurance Portability and Accountability Act requirements for patient confidentiality.

The DSTC meets twice a month. It is expected that members attend 75% of the biweekly meetings. Between meetings, the DSTC Chair or Co-Chair receives and reviews serious

toxicity reports and any significant serious medical alerts that require immediate action. The Chair has the authority to immediately suspend the protocol if there are concerns and issues that would affect patient safety. These actions are communicated to the PI, IRB, PRMC, CRO Medical Director and to the Associate Director for Clinical Research. DSTC recommendations to close a trial to accrual or terminate a trial are forwarded to the IRB, which has the authority to implement these actions. It is the PI responsibility (with support of the CTU or CRO) to communicate the DSTC actions to the study sponsor and other oversight agencies, as applicable and/or as dictated by a particular protocol. When necessary, the DSTC can call special meetings and/or appoint an additional group within the institution to assist in reviewing protocol data and quality assurance.

III.3.4 Conflict of Interest

DSTC members are subject to University Hospitals Cleveland Medical Center, Cleveland Clinic, and/or CWRU policies regarding standards of conduct based on their respective institution. Potential conflicts must be disclosed at least annually. PI, co-investigators, and any member of the study team listed on the protocol may be present during general discussion of the protocol and issues at DSTC meetings; however, they cannot participate in the evaluation and final decision making on that protocol in order to avoid the actual or potential conflict of interest. If PIs, co-investigators or any member of the study team serve as a DSTC member, they are expected to recuse themselves from voting. One of the DSTC members will temporarily replace the Chair if the Chair has to recuse himself/herself to avoid potential conflict of interest.

Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement of November, 2016, Pages I-14 and IIA-18, and 45 CFR Part 94.

Any potential conflict that develops during a member's participation on the DSTC must also be disclosed. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may continue to participate on the Committee are made in accordance with the respective institution's policies.

III.3.5 Review process of internal and external SAEs

The DSTC reviews SAEs in the following manner:

III.3.5.1 Internal SAEs are those SAEs experienced by subjects enrolled in trials that are located at site(s) coordinated by the Case CCC.

- SAEs occurring before the first day of treatment do not require reporting to the DSTC.
- All internal SAEs originating from either the TCI or the SCC will be reviewed at the meeting following their receipt by the DSTC.

- All SAEs from affiliate institutions of the trials that are coordinated by the Case CCC are considered by the DSTC to be internal, and are therefore reviewed at the meeting following their receipt to the DSTC.
- If immediate action is required for patient safety, the Chair or Co-Chair is advised and action is taken as appropriate.

III.3.5.2 External SAEs are considered those that are experienced by subjects that are enrolled in multicenter clinical trials at sites other than the sites over which the Case CCC DSTC has oversight.

- External reports in the form of Action Letters which are sent by industry sponsors are reviewed in terms of toxicities related to the investigational treatment that are on the same protocols as ones in which the Case CCC participates
- The respective CTU Regulatory Affairs Offices send the Action Letters that meet DSTC criteria for review to the DSTC.

III.3.5.3 General procedures

- Action Letters for trials coordinated by the Case CCC or that have reference to an agent being given to a patient treated at the Case CCC should be reviewed at the meeting following their receipt by the DSTC.
- It is the expectation of the DSTC that the PI will review all internal and external reports, and that the PI will provide these reports to the IRB as part of the continuing review.
- The DSTC reviews the relationship of the toxicity to the treatment that was assigned by the PI. The DSTC review determines whether the serious adverse event (SAE) requires action such as a request for more information on the SAE, or a request to the physician to consider changing the relationship of the attribution.
- The DSTC has the authority to suspend accrual to the trial if an early stopping rule endpoint is reached, or to suspend a trial based on excessive toxicity. Depending on the urgency of the recommendation, a committee meeting may not be required to review the status of a protocol. These actions are communicated to the PI, IRB, PRMC, CRO Medical Director and to the Associate Director for Clinical Research. DSTC recommendations to close a trial to accrual or terminate a trial, are forwarded to the IRB, which has the authority to implement these actions. It is the PI responsibility to communicate the DSTC actions to the study sponsor and other oversight agencies, as applicable and/or as dictated by a particular protocol. If the Case CCC is a leading institution on a trial the PI and/or study team will communicate the decision about study suspension and/or termination to site PIs and other IRBs, as applicable.
- The Chair of the DSTC is empowered to immediately suspend a trial for safety considerations. The decision to suspend or recommendation to close or terminate a trial is communicated to the PI, IRB, PRMC, CRO Medical Director and to the Associate Director for Clinical Research.

- It is the expectation of the DSTC that the IRB, sponsor, other relevant IRBs, NCI/CTEP, FDA, the Office of Biotechnology Affairs (for cell and gene therapy trials) and other oversight agencies, as applicable, are notified of all serious safety related events that require a protocol suspension, closure to accrual or termination based on toxicity issues.

III.4 Protocol-Specific Data and Safety Monitoring Plans

The institutional NCI-approved Cancer Center DSMP is designed to provide the essential elements of data safety and toxicity reporting for all institutional investigator-initiated interventional clinical trials. Protocol-specific DSMPs contain specific elements and are based on the Case CCC Monitoring Plan template (**Appendix C**) and state compliance with the Case CCC DSMP. If needed, there is an additional statement regarding the particular unique features of data and safety monitoring required for a given protocol based on the medical or health-related context of the trial, its degree of risk, the size of the trial, whether it is multicenter, and whether review after first patient accrual is required based on the novelty of treatment intervention or the degree of risk.

The PRMC ensures that all protocols have an adequate DSMP and the review of the DSMP is included in the review of each protocol. The PRMC does not approve trials until the DSMP is reviewed.

III.5 Oversight and Management of Conflict of Interest

To manage the inherent conflict of interest of toxicity reports being reviewed and prepared by the PI, appropriate checks and balances exist to ensure appropriate review and reporting of such toxicities. This includes research nurse preparation of toxicity reports, review of toxicities by the DSTC, and communication of DSTC actions to the PI, IRB, PRMC, CRO Medical Director and the Associate Director for Clinical Research.

III.6 Reporting of Serious Adverse Events

Serious adverse events are reported and reviewed at the DSTC meetings. Reportable SAEs are defined by the protocol using guidelines of the NCI Common Terminology Criteria for Adverse Events, the sponsor's system of reporting as outlined in the *Case CCC Clinical Trials Operations Manual* and by IRB guidelines. To ensure that SAE report requirements are met, the DSTC maintains a log of SAEs with the date of occurrence. The OnCore® serves as a centralized database for clinical trial and patient-related data for Case CCC participating institutions. The OnCore® database allows for reconciliation between submission to the PRMC, IRB, DSTC, and CTUs to ensure that all applicable federal, state and local requirements are met. The logs are reviewed at the DSTC meetings to assure compliance with reporting requirements. Variances in reporting are reported by the DSTC to the CRO Medical Director and to the Associate Director for Clinical Research. If necessary, a Corrective Action Plan (CAP) will be required to be developed by the CTU and the PI to ensure adequate and timely SAE reporting.

Serious adverse events are recorded by the research nurses, reviewed by the attending physician and by the PI and submitted by the CTUs to the DSTC; IRB; sponsor, as per contract; collaborating institutions for appropriate investigator-initiated Case CCC-led multicenter trials; the FDA and the NCI (for CTEP-sponsored trials and those with NCI funding); and the NIH/OBA (for cell and gene therapy studies).

For high risk trials, a separate set of reviewers is assigned to audit all data emanating from the clinical trials. An example would be a gene therapy clinical trial with laboratory production of genetically altered cells for infusion. In this instance, the CTUs will audit the primary laboratory data for accuracy, completeness and study endpoints.

Adverse event reporting requirements vary between protocols. Each protocol clearly states the requirements for adverse event reporting. The PI monitors these reporting events to ensure their timeliness, accuracy and that all appropriate entities have been informed.

The CTUs comply with all sponsors and their reporting needs. All study coordinators and research nurses are trained in SAE identification and reporting, and all protocols requiring AE reporting are identified prior to activation. The CTUs also participate in NCI Clinical Data Update System (CDUS) reporting as required by specific NCI-sponsored trials providing the sponsor with a summary of quality information including adverse or unexpected events.

III.7 Communication to NCI of Temporary or Permanent Suspension of Clinical Trial Protocols Funded by the NCI

It is the policy of the Case CCC that all actions affecting the accrual status of a clinical trial, including temporary protocol suspension and protocol termination are reported to the appropriate NCI Program Director. Each protocol funded by the NCI is registered in OnCore®. The PI and the CTUs have responsibility for adequate reporting to the NCI Grant Program Director. Such reports are also submitted to the DSTC. Failure to report will be noted by the DSTC, and a CAP will be required to be developed by the CTU and the PI. This reporting requirement includes any FDA actions that effect NCI trials, actions recommended by the IRB, a sponsor, or the NCI itself. If reports are deficient, the DTSC will request the PI to provide an amendment. If reports or amendments are not adequate and/or completed in a timely fashion, the DSTC has the authority to suspend a trial.

III.8 Protocol Suspension or Termination

Reasons for protocol suspension or termination may include the following:

- a. accrual goal met;
- b. stopping rules activated due to:
 - i. the dose escalation has reached the DLT or the maximum tolerated dose, as indicated by the protocol;
 - ii. excessive toxicity and/or;

- iii interim analysis of two-stage design indicates a response above or below the margins outlined in the trial;
- c. accrual rate deficient and correction action not effective;
- d. DSTC has concerns about protocol compliance or ability of the PI to continue to meet local or federal regulations.

Recommendations to make clinical trial changes, to hold accrual, and to suspend and/or terminate a clinical trial in which it is determined that continued accrual or treatment would place patients at risk, may come from the PI, IRB, DSTC, PRMC, review and monitoring committees for high risk clinical trials, Biostatistics Core Facility members, the Associate Director for Clinical Research and the Case CCC Director.

These recommendations may be brought forward to the IRB, DSTC, and PRMC. The DSTC may immediately suspend a trial and notify the PI, IRB, PRMC, CRO Medical Director and to the Associate Director for Clinical Research. The PRMC may close or terminate a trial due to inadequate accrual or failure to meet the objectives of the study. The IRB has the final authority to close a trial to accrual or terminate a trial for subject safety

During the course of a clinical trial, recommendation for protocol suspension can be also made by the sponsor, NCI, or the NCTN. If an action is required before DSTC or PRMC can convene, recommendation for suspension can be directed either to the respective committee Chair and/or to the Associate Director for Clinical Research. Otherwise, the recommendation is considered at the next scheduled meeting of whichever committee meeting comes first.

III.9 Plans for Assuring Data Accuracy and Protocol Compliance

III.9.1 Role of the Biostatistics Shared Resource in Quality Assurance

The Biostatistics Shared Resource members monitor accrual and other events relevant to planned interim analyses and protocol-defined stopping rules, providing documentation and determining whether formal stopping rule boundaries have been reached. The Biostatistics Shared Resource members may be also asked to assist in randomly selecting a specified number of charts for internal reviews. The QA monitoring and review schedules follow the monitoring plan.

III.9.2 OnCore® Clinical Trials Management System

The Case CCC uses the OnCore® Clinical Trials Management System which serves as a centralized database for clinical trial patient-related data for Case CCC participating institutions. The Case CCC requires that data on all cancer clinical trial accruals is entered into this database. The internet-based Clinical Trials Management System was developed by PercipEnz, Inc. Data entry is accomplished online using web-based forms, consoles and entry screens. Case CCC staff also utilizes OnCore® for accurate and timely reporting on protocol and patient-related information.

III.9.2.1 Database Edit Checking and Security

Edit checks for valid entry are done during the process of data entry. Additional edit checks and cross validations are run separately during monitoring interim visits. The web-based case report forms and entry screens have been designed specifically for the needs of Case CCC researchers and the CTUs. Standardized pull-down lists are used when appropriate to facilitate data entry and reduce error. The OnCore® system allows access from multiple sites, including Case CCC, SCC and TCI, satellite clinical sites in the community, as well as other affiliated institutions. Users are trained and given appropriate system access and permissions. In the secure OnCore® system, each user account has a specific access level reflecting the user's role within the Case CCC and his/her needs. This particular privilege is verified and assigned by the OnCore® administrator. Users can perform authorized operations (e.g. inserts and/or updates) to records as per their access granted by the administrator. Lead personnel in the CTUs can lock data records so they cannot be modified. The OnCore® application has the following features: (1) a two-factor authentication system for users to log into a secure server, resulting in improved protection of protocol information (2) system audit tables are maintained to track when a user logs in and out of the system; and (3) application audit tables are maintained to track changes made to the database itself. The OnCore® database is characterized by the ease of use, accuracy, completeness, timeliness, security, flexibility, and efficiency.

III.9.3 Role of the CRO in Quality Assurance and Quality Control

The Case CCC has initiated several processes aimed at meeting NCI guidelines and requirements, becoming early participants in new NCI initiatives and maintaining a high quality management and oversight of the clinical trials that are conducted at the Case CCC.

The CTWG authors SOPs and policies related to maintaining consistency and high quality for the conduct of the Case CCC clinical trials. The CTWG requires approval of the C-ROC for all new SOPs and policies. The SOP Manual is available on the Case CCC website at: <http://cancer.case.edu/research/clinical-research-office/>.

Jointly, the Quality Assurance (QA) staff of the CTUs have created and implemented a monitoring SOP consisting of monitoring guidelines, training, and templates (**Appendix C**). Additionally members of the QA teams at consortium institutions are members of the CTWG and DSTC, and participate in CTWG meetings. CTU staff focus quality assurance efforts on all investigator-initiated interventional trials. Specifically, the trials are prioritized where a Case CCC PI holds the IND/IDE and takes on the responsibilities as the Sponsor-Investigator. Both QA teams jointly participate in continuing education and training for monitoring of investigator-initiated IND/IDE trials.

QA monitoring for each clinical trial opened jointly at both consortium sites is managed across sites by a standardized monitoring plan which is created by the lead institution (in most instances, the lead institution is determined based on the institution where the PI is based), and shared with the second institution. The plan addresses protocol monitoring from the site

initiation visit through the close out visit, covering data integrity, regulatory, and pharmacy, and defining minimum criteria to be monitored. Lead QA representatives meet on a monthly basis to discuss any challenges, progress, and successes. Additionally, any changes to federal regulations or guidances as well as to institutional policies that may affect operations or quality initiatives are discussed and SOPs and processes are adjusted accordingly.

Joint Site Initiation Visits (SIV) are conducted as new investigator-initiated trials are activated. A template document has been created and used to educate staff attending the SIVs. This document also serves as an educational tool for staff that joins the trial during the life of the study. Additional orientation and training for SIV initiation is conducted across the Case CCC on an as needed basis.

Joint orientation for both SCC and TCI CTU staff set the standards for education and provide a structure for ensuring adequate training of Case CCC staff participating in the clinical research process. The CTWG provides joint continuing education to all research study staff. These joint sessions provide a centralized format for educating and training staff on Case CCC policies, SOPs and best practices, as well as, for working sessions for functional groups.

III.9.3.1 Registration On-Study

Study coordinators must submit for review all proposed study patients for consent validation and eligibility verification before registration. At screening, the research nurse/study coordinator fills out an Inclusion/Exclusion worksheet for the potential patient, indicating each Inclusion and Exclusion criteria response, ensuring that source documentation for each criterion is available. Once the Inclusion/Exclusion worksheet is completed, it is forwarded to a Quality Assurance team member (at SCC CTU) or to another nurse (at TCI CTU) for review and signature. At TCI, if another person, as applicable, is not available, a co-investigator may review and sign the eligibility. At both sites, the site PI or co-investigator must confirm eligibility status by signing and dating the Inclusion/Exclusion worksheet prior to the patient registration. A total of three signatures are required for the study eligibility confirmation and one must be the PI or co-investigator. In the case of patient screen failures, only one signature is required. If consensus agreement on patient eligibility is not met, the institute/program research director or designee or CTU Medical Director, who is not an investigator on the study, will make the final determination.

Registration must be completed before treatment unless stated in the protocol (for instance, a leukemia protocol requiring urgent treatment that so indicates this exception in the protocol). Eligibility items are reviewed against source documents in the medical records.

III.9.3.2 Quality Control Monitoring

Monitoring visits are conducted in the interest of improving quality control, protocol compliance, and data management procedures. Specifically for investigator-initiated trials, the first patient

enrolled on the trial as well as at least 10% of all accruals are monitored. This retrospective review is conducted by Quality Assurance personnel not directly associated with the protocol.

Investigator-initiated interventional clinical trials are selected based on risk and the frequency of monitoring is based on the monitoring plan. All studies in which a Case CCC investigator holds the IND/IDE, Case CCC manufactures the study agent, or Case CCC-led multicenter trials are considered high risk. Other investigator-initiated interventional clinical trials are monitored on a less frequent basis at SCC CTU, and at TCI CTU these studies will have Quality Assessment visits (i.e. similar to an audit but performed by Cleveland Clinic staff and not an external entity) performed instead of monitoring visits. The investigator-initiated studies are monitored for study conduct, protocol compliance, integrity of data, and regulatory, pharmacy and subject issues.

The PRMC monitors study progress in terms of accrual every 6 months. The DSTC reviews all other aspects of study progress when reviewing continuing review reports.

Monitors and oversight committees ensure that clinical trials are conducted in compliance with protocols and with all applicable guidelines, policies and procedures, and federal regulations. They detect trends and/or system errors that may lead to non-compliance or risk to participants and ensure that CAPs are implemented and followed. Through interactions with investigators and research staff, they educate the research community and promote high and consistent clinical research standards.

Monitors review the following: 1) patient eligibility; 2) SAEs to ensure that all have been reported to applicable agencies in a timely fashion; 3) drug doses to ensure that they were modified as per protocol; 4) safety testing (laboratory tests and other procedures that impact dose modifications and patient continuation on a study) to ensure that it was performed as per protocol; 5) pharmacy records and storage; and 6) regulatory records.

Scores are assigned to each review category deeming it acceptable, acceptable with follow-up, unacceptable or not applicable. Monitoring visits are reported to the PI and the study team.

Copies of the quality assessment and monitoring reports are kept in the respective CTU office. Results are discussed with the study PI. If significant findings are discovered which could affect patient safety and/or trial integrity, the issues would be forwarded to DSTC, CRO Medical Director, Associate Director for Clinical Research and to the Case CCC Director, as applicable, for review/action.

The DSTC reviews and monitors the following: 1) all internal SAEs; 2) all Action Letters; 3) SAEs from trials which are coordinated and led by Case CCC investigators; 4) continuing reviews for trial progress and safety (before continuing reviews are reviewed and approved by the IRB). At the time of continuing review, the DSTC focuses on, among other items, protocol-

wide issues such risk-benefit profile, potential higher frequency of errors, protocol deviations and violations, and the number of patients and reasons for withdrawal; 5) audit reports and CAPs; 6) confirmation of responses; 7) timeliness of the reporting to the IRB; 8) trends in events such as SAEs and/or deviations/violations; and 9) early stopping rules.

III.9.3.3 Internal Quality Assessment/Monitoring of High Risk Trials

Investigator-initiated trials that are deemed high risk trials will require first patient review/monitoring which is performed after at least 2 cycles (or other appropriate milestone to evaluate study compliance and safety). The respective CTU QA staff review the laboratory records, pharmacy records and treatment records to ensure that there is compliance with protocol guidelines, reporting procedures and toxicity reporting. Depending on the decision made, the trial and/or further enrollment may be modified.

Copies of the quality assessment reports are kept in the respective CTU offices. Results are discussed with the study PI. If significant findings are discovered which could affect patient safety and/or trial integrity, the issues would be forwarded to DSTC, CRO Medical Director, Associate Director for Clinical Research and to the Case CCC Director, as applicable, for review/action.

Audits of clinical trials are performed by the UH Center for Clinical Research when randomly or when requested by the CTU or PI. The Cleveland Clinic Center for Clinical Research performs quality assessments for studies in which the PI holds the IND/IDE.

III.9.4 Data and Safety Monitoring Board

A Data Safety and Monitoring Board (DSMB) is an independent, impartial group of experts that periodically reviews and evaluates accumulated trial data for participant safety, trial conduct and progress; and makes recommendations to the trial investigators concerning the continuation, modification or termination of the trial when significant benefits or risks have been uncovered or when it appears that the clinical trial cannot be concluded successfully. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The National Institutes of Health (NIH) requires data and safety monitoring, generally, in the form of DSMBs for phase III clinical trials, especially for investigator-initiated randomized phase III clinical trials. For earlier trials (phase I and II), a DSMB may be appropriate if the studies have multiple clinical sites, are blinded, or employ particularly high-risk interventions or vulnerable populations. A DSMB might be considered for practical reasons such as for trials with a high chance of early termination for safety or efficacy reasons, or to have an independent review group that may help to add validity to the trial.

NIH policy provides the flexibility to implement the requirement for data and safety monitoring as appropriate for its clinical research activities. More information about those policies can be found at:

- <https://grants.nih.gov/grants/guide/notice-files/not98-084.html>

- <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>
- <https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf>

The Case CCC requires a DSMB for phase III or large phase II, randomized, multi-site clinical trials involving interventions that entail potential risk to the participants. If not specified in the protocol, the Case CCC PRMC will identify studies which require establishment of an *ad hoc* DSMB and the Case CCC leadership will appoint the voting members, who are free of any conflict of interest, as per NIH guidelines. The DSMB will determine the frequency of its meetings and review (not less than semi-annually) on a study-by-study basis. The DSMB will forward its reports to the Case CCC DSTC, C-ROC, IRB(s) and PI(s), as applicable.

III.9.5 Multicenter Trials and Randomized, Blinded Trials

Case CCC investigator-initiated Phase II multicenter trials require a consortium agreement developed by the Cancer Center that defines monitoring and toxicity reporting, and indicates the reporting frequency. The toxicity reporting requirements match those for Phase I and Phase II trials as appropriate. Serious adverse event reporting by each site includes notification to the Case CCC as well as the appropriate reporting agencies.

Monitoring and audits of multicenter trials include review of all primary source documents either during a site visit or via submission of the documents by fax or secure method. SAE reporting is monitored by the PI with the assistance of a multi-site coordinator. The monitoring/audits are performed as outlined above, with the added emphasis on SAE reporting to the DSTC.

Case CCC phase II trials with randomized, blinded intervention assignments that do not have a DSMB will have an unblinded and blinded statistician as well as an honest broker, i.e. an individual unrelated to the study conduct, who will view unblinded data as needed. Monitoring of blinded studies will involve a QA coordinator to review randomization and pharmacy records, i.e. for accuracy of drug dispensation and return, and another QA coordinator to review all other aspects of study conduct.

Investigator-initiated randomized Phase III and large phase II trials that otherwise do not have an independent DSMB assigned require an individualized DSMB that is convened prior to the initiation of the trial. These trials include both NCI- and industry-sponsored large randomized studies, typically Phase III trials, which have a Case CCC investigator as the lead investigator. The DSMB has the responsibility of data and safety monitoring and has the authority to recommend protocol amendments and closure based on its independent audit. The DSMB is a group of independent experts typically not related to the parent institution or the protocol sponsors and it is established as per NIH guidelines for DSMBs.

III.9.6 National Clinical Trials Network and Industry Sponsored Trials

Patients accrued to National Clinical Trials Network (NCTN) (SWOG, ECOG/ACRIN, NRG, COG, Alliance) or to industry-sponsored trials protocols are subject to case evaluation,

pathology verification, radiation field quality control and data query. All patients enrolled have a second review of eligibility prior to registration.

The CTUs are normally audited on a three-year cycle by an independent review team from the NCTN on a randomly selected pool of accrued patients. The results of each audit determine the subsequent review cycle and in some circumstances, more frequent audits could occur.

The CTUs are subject to routine and regular monitoring by the sponsor (or the Clinical Research Organization on industry sponsored trials. For all external audits, the CTUs prepare primary source documents.

All external audit reports are reviewed by the PI, Administrative and Medical Directors of the respective CTUs and DSTC. Audit information is listed in DSTC meeting minutes which are provided to the PRMC, CTU Medical Directors, CRO Medical Director and Administrative Director, and Associate Director for Clinical Research. Any issues deemed significant are escalated to, the Case CCC Associate Director for Clinical Research and to the Case CCC Director, as applicable, for review/action.

III.9.7 Corrective Actions and Resolution Process

When necessary, deficiencies in patient management, toxicity reporting, data accuracy, etc., will be noted and a plan will be developed with the CTU, the research nurse, and the PI to correct the deficiencies noted. These plans will be forwarded to the DSTC and/or, PRMC, and, when appropriate, to the study sponsor.

External audits follow the process established and required by an auditing body. Reports, responses and CAPs for external audits are submitted and reviewed by the DSTC.

The DSTC may accept the PI's response and CAP and will notify the PI accordingly. If the items are not resolved, the DSTC may request that further steps are taken to address the issues. A memo will be sent to the PI requesting additional information and/or a revised plan for a better resolution of outstanding issues. Findings that are considered to have a potential significant negative impact on patient safety and/or integrity of the results will be reported to the Case CCC Associate Director for Clinical Research and may require response within a shorter timeframe. Any findings which may indicate a potential scientific misconduct would be reported immediately to the Case CCC Director, Associate Director for Clinical Research, Deputy Associate Director for Clinical Research/Director of Clinical Trials, and would be subject to University Hospital Cleveland Medical Center, Cleveland Clinic, and/or Case Western Reserve University policies regarding scientific misconduct based on the respective institution.

If investigators disagree with the auditor's report and/or DSTC determination, they can respond to the items as they deem appropriate. Responses detailing resolutions that are not adequate or different to those suggested by the auditor and/or DSTC would be acceptable *if* they are

sufficiently explained and justified. It is up to the auditor and/or DSTC to accept them or request a follow-up.

If the PI wishes to appeal DSTC decision/action, the request should be made in writing to the Case CCC Associate Director for Clinical Research, who will mediate a discussion with the PI, DSTC and all involved parties. If a consensus resolution cannot be reached, the DSTC decision will be final, as long as it is not in the direct violation of the federal, state, institutional and local IRB regulations and policies.

IV. APPENDICES

Appendix A(1): University Hospitals Cleveland Medical Center IRB: Reporting of Adverse Events and Unanticipated Problems (January 2016)

Appendix A(2) and A(3): Cleveland Clinic IRB: IRB-60: Adverse Event Reporting (3/15/12) and IRB-70: Reporting Unanticipated Problems (8/27/14)

Appendix A(4): Case Western Reserve University IRB: Event Reporting – Unanticipated Problems, Adverse Events, and Protocol Deviations (10/2015)

Appendix B: Case CCC SOP: PRMC-10.3.0; Version 3.0; 4/7/15: Protocol Review and Monitoring Committee Accrual Monitoring

Appendix C: Case CCC SOP: QA-8.1.0; Version 3.0; 5/5/15: Monitoring Investigator-Initiated Clinical Trials with attachments

Appendix D: Case CCC Data and Safety Monitoring Plan Reporting Summary (March 2015)

Appendix E: Case CCC Protocol Review and Monitoring Committee Roster (February 2017)

Appendix F: Case CCC Data Safety and Toxicity Committee Roster (February 2017)