

**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
CT.gov	ClinicalTrials.gov
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: <https://case.edu/cancer/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.

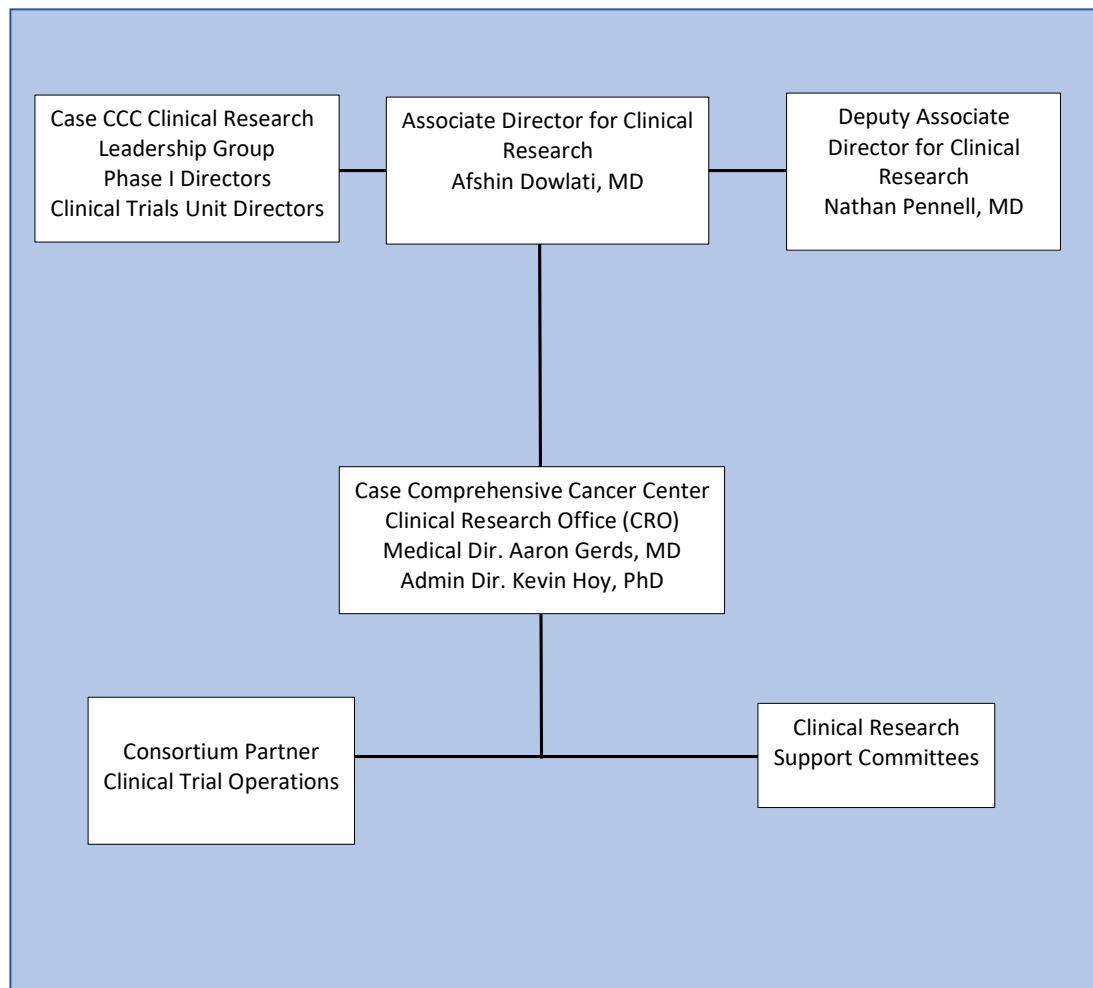
I.1.5 Gene Transfer Studies

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 management system, 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: <https://case.edu/cancer/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, social behavioral 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, 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 or archival tissue 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 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 all 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. For Case CCC investigator-initiated studies 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. For sponsored studies the IRBs review for their respective sites.

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. The study status is updated in OnCore® on an on-going basis to facilitate tracking by PRMC, PIs and regulatory coordinators. The registration process also acts as the initial registration point for ClinicalTrials.gov (CT.gov) and CTRP databases. 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, these events should also be updated in OnCore for results reporting in CT.gov; 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. All SAEs must be updated and verified in OnCore at the time of reporting. 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. All interventional studies are required to be registered in the in CT.gov by the CRO office in coordination with the study team before the first participant is accrued to the study.

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. In addition, the committee should verify that these items are entered in OnCore.
- Monitor timely endpoint collection – particularly for slow accruing studies to ensure readiness of data for CT.gov reporting.
- 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 DSTC 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 Forte 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: <https://case.edu/cancer/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 guidance 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 (July 2020)

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; 4/20/20: 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 (October 2016)

Appendix E: Case CCC Protocol Review and Monitoring Committee Roster (July 2020)

Appendix F: Case CCC Data Safety and Toxicity Committee Roster (August 2020)

Chapter 20- Reportable New Information

Investigators and study team members may submit Reportable New Information (RNI) to the IRB. Please note: the author of the RNI will be listed as the point of contact for the RNI submission and all communication will occur between the IRB and that individual.

A member of the study team must complete and submit the Report New Information SmartForm within **five business days** for any of the following information items:

- Information that indicates a new or increased risk, or a new safety issue. For example:
 - New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) that indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.
 - An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk
 - Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol
 - Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm*
 - Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm*
 - Any changes significantly affecting the conduct of the research
 - Any adverse event, which in the opinion of the PI, are **both** unexpected and related or possibly related to the study/study participation and involves increased risk to the subject or others is considered an unanticipated problem.*
 - An adverse event is “unexpected” when its specificity or severity are not accurately reflected in the IRB approved informed consent document or protocol, or are not expected given the characteristics of the subject population being studied
 - An adverse event is “related to the research procedures” if in the opinion of the PI, it was more likely than not to be caused by the research procedures, or if it is more likely than not that the event affects the rights and welfare of current participants. Non-compliance with the federal regulations governing human subjects research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.*
- Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g. FDA Form 483.)
- Written reports of study monitors if applicable to IRB
- Major failure to follow the protocol due to the action or inaction of the investigator or research staff.*
- Breach of confidentiality.*

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- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.*
- Incarceration of a subject in a study not approved by the IRB to involve prisoners.*
- Complaint of a subject that cannot be resolved by the research team.*
- Premature suspension or termination of the protocol by the sponsor, investigator, or institution.
- Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.*
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Event that requires prompt reporting to the sponsor such as disqualification or suspension of investigator.

*Reporting required for internal events only.

Internal encompasses events that occurs in a participant who was consented using a UHCMC IRB approved consent process. Studies approved by the UH IRB but conducted outside the United States are considered “internal” for adverse event reporting.

External encompasses events reported to a UHCMC investigator that occurred in a participant who gave consent using consent documents that were not approved by the UHCMC IRB.

External events where the UHCMC investigator is not responsible for the reporting of the event to a regulatory agency are expected to have review as described in the Data and Safety Monitoring Plan (DSMP) for the protocol. All external events reported to a UHCMC PI must be promptly reviewed by the PI and any event that changes the risk/benefit ratio of the study must be reported as information that indicates a new or increased risk. If protocol or consent form changes must be made due to a revised risk profile those changes should be submitted to the IRB as soon as possible.

All internal, unexpected, study-related deaths must be reported to the IRB within five business days of their discovery. Both internal, expected, study-related or non-study-related deaths and internal, unexpected, but not study-related deaths should be retained in the Principal Investigator files.

Failure to report in a timely manner may be considered a compliance matter and referred to the IRB for review and a compliance determination.

Any event that does not fit into the above categories does not require reporting on an RNI form. Please review the section regarding Continuing Reviews for additional reporting guidelines.

Protocol Deviations

A PI with an IRB approved protocol must conduct the protocol under the terms and specifications of the study as approved by the IRB. An investigator may not deviate from the requirements for procedures or testing of participants as outlined in the protocol. Protocol Deviations must be reported by the PI to the IRB in a timely manner. Major Deviations are reported to the IRB within five business days of discovery. Minor Deviations are kept in the investigator's file to be reported at the time of continuing review.

Deviations are reported electronically using the appropriate category on the RNI form. Frequently, the most appropriate category is "Non-compliance" or "Researcher error," but this is not all-inclusive and other categories may be more applicable depending on the nature of the situation. The author of the RNI should briefly explain the new information and the corrective actions taken to avoid future deviations. If a change in the protocol is needed, questions 5b) and 5c) should be answered appropriately and the PI will submit a protocol amendment electronically in the electronic system. The examples listed below are a guide and are not meant to be all-inclusive.

1) Examples of Major Deviations

- Failure to obtain informed consent, i.e., there is no documentation of informed consent or informed consent was obtained after initiation of study procedures;
- Informed consent obtained by someone not approved to obtain consent for the protocol;
- Use of invalid consent form, i.e. consent form without IRB approval;
- Enrollment of a participant who was ineligible for the study;
- Performing a research procedure not in the approved protocol;
- Failure to report serious adverse event to IRB; sponsor; and/or regulatory agencies;
- Study medication dispensing or dosing error;
- Failure to follow the approved study protocol that affects participant safety or data integrity (e.g., study visit missed or conducted outside of required timeframe, or failure to perform a laboratory test);
- Failure to follow safety monitoring plan;
- Continuing research activities after IRB approval has expired;
- Use of recruitment procedures that have not been approved by the IRB;
- Participant giving study medication to a third-party;
- Enrolling significantly more subjects than proposed in the IRB protocol;
- Any deviation that impacts the risk / benefit ratio;

2) Examples of Minor Deviations

- Missing original signed and dated consent form (only a photocopy available);
- Missing pages of executed consent form;
- Failure to follow the approved study protocol that does not affect participant safety.(e.g., study procedure conducted out of sequence, failure to perform a required test, missing laboratory results, study visit conducted outside of required timeframe.);
- Use of consent forms that are outdated/expired but contain the same information as the current consent;

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- Failure of a participant to return study medication.

All protocol deviations are initially reviewed by the IRB Chair or a Vice-Chair and sent for Board review as required. Board determinations will be reported to outside agencies as required. Study sponsors may have different reporting requirements than the IRB and it is the PI's responsibility to be knowledgeable about, and meet, the study reporting requirements.

Any other event that does not meet criteria of an unanticipated problem or a study-related event causing harm or increasing risk to participants does not require prompt reporting on an RNI form. Please review the section regarding Continuing Reviews for additional reporting guidelines.

IRB-60

Adverse Event Reporting

POLICY:

The Institutional Review Board requires Investigators to monitor and report Adverse Events. The Institutional Review Board is responsible to assess changes in risk to ensure safety protections of human subjects

DEFINITIONS

An **Unanticipated Problem Involving Risks to Participants or Others** is any event that (1) is unforeseen, (2) caused harm or placed a person at increased risk of harm, and (3) is related to the research procedures.

An **Adverse Event (AE)** is any untoward or unfavorable medical occurrence, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptoms, or disease. Adverse events encompass both physical and psychological harms.

An **Internal Adverse Event (AE)** is an untoward medical occurrence, which occurs to participants in research conducted by Cleveland Clinic and/or Cleveland Clinic is the IRB of record.

An **External Adverse Event (AE)** is an untoward medical occurrence experienced by subjects enrolled at other institutions for the same study approved at Cleveland Clinic or a different study using the same study drug/device.

A **Serious Adverse Event (SAE)** is any adverse experience that results in any of the following outcomes:

- death
- a life-threatening experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An **Unexpected Adverse Event** means any AE not previously known or included in the current Investigator's Brochure, consent form or other risk information.

Related/Possibly Related means there must be reasonable evidence to suggest the event was caused by the drug, device or investigational intervention.

PROCEDURES:

1. **Internal Serious Adverse Events** (events that occur to participants enrolled in research being conducted by Cleveland Clinic) must be promptly reported to the IRB using the IRB AE Report Form within **10 working days** from discovery/awareness which meet any of the following criteria as assessed by the PI/Co-I:
 - a) Serious, Unexpected and Related/Possibly Related.
 - b) AE's determined to be occurring at a significantly higher frequency or severity than expected.
 - c) Other Unexpected AE's, regardless of severity, that changes the risk benefit ratio of the study and results in changes to the Research Protocol or Informed Consent process/document.

All Internal SAEs are also reported at **continuing review** using the AE Summary Log.

2. **External Serious Adverse Events** (events experienced by subjects enrolled at other institutions for the same study approved at Cleveland Clinic or a different study using the same study device/drug) are reportable to the IRB using the IRB AE Report Form within **10 working days** from discovery/awareness when:

- a. **The External SAEs report must include reasonable evidence** from the entire safety database as assessed by a central monitoring entity [Coordinating or Statistical Center, or a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC)] that the event is Serious, Unexpected, and Related/Possibly Related **AND** places the subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. This will require a change in the protocol and/or consent document.
- b. **External SAEs** reports not meeting the above criteria are reported at continuing review on the AE Summary log.
- c. **External SAEs** from **a different study** using the same drug/device **NOT** meeting the above criteria are not reportable to the IRB.

3. **DEATHS** are to be reported to the IRB using the IRB AE Report Form according to the following guidelines:

- a) **Internal Death**

- Related/possibly related whether expected or unexpected– within 5 working days from discovery/awareness
- not related and expected – at time of continuing review
- Cancer studies - not related and unexpected within 10 working days from discovery/awareness

b) External Death

- Related/possibly related and unexpected – within 5 working days from discovery/awareness
- not related whether expected or unexpected – at time of continuing review
- related/possibly related and expected – at time of continuing review

c) ALL Deaths are also reported **at time of continuing review** using the AE summary log.

4. **Non-serious Adverse events (Internal and External)** that are both Related/Possibly related and Unexpected are reported on the **AE Summary Log** at time of continuing review to assess trends.

Cancer AEs that are Graded 1 or 2 are separately reported and assessed through the Cooperative Groups, CTEP or Oncore and are not included in the AE Summary Log.

5. An IRB staff (a qualified, licensed practitioner assigned to this function by the IRB chair and IRB Executive Director) reviews Adverse Event Reports to determine whether they represent Unanticipated Problem Involving Risks to Participants or Others. Events that are assessed, by either the IRB Staff or Investigator, to place subjects or others at a greater risk of harm than was previously known or recognized, or changes the risk/benefit ratio of the study, or requires a change in the protocol and/or consent document are referred to Full Board for review under Policy #70.

Events that do not involve risk to Participants or Others or changes to the informed consent or protocol do not require further review. Investigators are informed of the determination and the IRB file is updated.

6. The AE Summary Log is reviewed by the IRB at the time of continuing review to identify trends in frequency and severity which may impact subject safety.

Revised: 05/01/02, 6/13/02, 10/23/02, 10/29/02, 12/05/02, 02/13/03, 08/04/03, 10/14/03, 11/19/03, 3/03/05, 5/15/06, 6/7/06, 6/14/06, 6/3/2009, **3/15/12**

Table 1

Internal Adverse Events

Significance of Adverse Event	Study Related (Related/Possibly Related)		Not Study Related (Unrelated/Unlikely)	
	Expected	Unexpected	Expected	Unexpected
Deaths Cancer: Fatal Events (Grade 5)	5 working days And Summarize in continuing review report	5 working days And Summarize in continuing review report	Summarize in continuing review report	Summarize in continuing review report And Cancer must also submit in 10 working days
Serious Cancer: Life-threatening (Grade 4) or Severe/undesirable (Grade 3)	Summarize in continuing review report	10 working days And Summarize in continuing review report	Summarize in continuing review report	Summarize in continuing review report
Adverse Events (non-cancer studies)	Not reportable to IRB	Summarize in continuing review report	Not reportable to IRB	Not reportable to IRB
Cancer: (Grades 1 & 2)	Not reportable Unless otherwise specified by protocol			

*All study related, unexpected deaths should be carefully assessed against the definition of unanticipated problem.

Working days means from awareness/discovery

Table 2

External Adverse Events

Significance of Adverse Event	Study Related (Related/Possibly Related)		Not Study Related (Unrelated/Unlikely)	
	Expected	Unexpected	Expected	Unexpected
Deaths Cancer: Fatal Events (Grade 5)	Summarize in continuing review report	5 working days And Summarize in continuing review report	Summarize in continuing review report	Summarize in continuing review report
Serious Cancer: Life-threatening (Grade 4) or Severe/undesirable (Grade 3)	Not reportable to IRB	Summarize in continuing review report Unless risk is increased (10 working days) *	Not reportable to IRB	Not reportable to IRB
Adverse Events (non-cancer studies)	Not reportable to IRB	Summarize in continuing review report	Not reportable to IRB	Not reportable to IRB
Cancer: (Grades 1 & 2)	Not reportable Unless otherwise specified in protocol			

* SAE's that change the risk/benefit ratio or result in changes to consent must be reported to the IRB within 10 working days.

Working days means from awareness/discovery

Adverse Event Summary Log

IRB #: _____

Study Title: _____

☐ Check here if there are no reported SAE/AE for this study[illegible]

IRB- 70

Reporting Unanticipated Problems Involving Risks to Participants and Others

POLICY:

The IRB requires Investigators to promptly report unanticipated problems involving risk to participants or others. The IRB assesses whether the event is unanticipated, related or possibly related to participation in the research and whether the research places participants or others at a greater risk of harm (physical, psychological, economic, or social harm) not previously recognized or has a significant effect on the scientific soundness of the research plan. IRB determinations of unanticipated problems involving risk to participants or others are reportable to appropriate institutional officials and federal authorities if applicable.

DEFINITIONS:

Unanticipated Problem (UP) Involving Risks to Participants or Others includes any event, incident, experience, or outcome that meets all of the following criteria:

- (1) **unexpected** (in terms of nature, severity or frequency) given (a) the research procedures described in the protocol and/or informed consent document and (b) the characteristics of the subject population being studied;
- (2) **related or possibly related** (reasonable possibility) that the incident, experience, or outcome may have been caused by the procedure involved in the research, and
- (3) the incident, experience, or outcome **places subjects or others at a greater risk of harm** (including physical, psychological, economic or social harm) than was previously known or recognized or has a **significant effect** on the scientific soundness of the research plan.

Unanticipated Problems Involving Risks generally warrant consideration of substantive changes in the research protocol, consent process/document or other corrective action in order to protect the safety, welfare, or rights of subjects or others to ensure the scientific soundness of the research.

Adverse events that are serious, unexpected and related/possibly related to the research may represent an unanticipated problem involving risk and are to be reported to the IRB using the Adverse Event Report Form. See IRB Policy 60 “Adverse Event Reporting.”

Breach of Confidentiality – includes inappropriate disclosure of PHI to a third party outside the institution, lost or stolen laptop, external devices or research files containing PHI.

Protocol Deviation - a departure from the IRB approved protocol or consent process. Whether a deviation represents an unanticipated problem involving risks to participants and others depends upon the event having a **significant effect** on the rights, safety, or welfare of human subjects or scientific soundness of the research plan. Deviations may be classified as Major or Minor based upon the impact on subjects and the research plan.

MAJOR Protocol Deviation – a deviation, based on the clinical judgment of the PI or their designee, determined to **significantly impact** the scientific soundness of the research plan or suggest the research placed participants or others at a greater risk of harm (physical, psychological, economic, or social harm) not previously recognized. A major deviation **meets all criteria** for an UP involving risk.

MINOR Protocol Deviation – a deviation that **does not significantly impact** the scientific soundness of the research plan or suggest the research placed participants or others at a greater risk of harm (physical, psychological, economic, or social harm) not previously recognized.

Deviations caused by Participants – a deviation caused by the participant, can be either major or minor depending if the deviation does or does not significantly impact the scientific soundness of the research plan or suggest the research placed participants or others at a greater risk of harm (physical, psychological, economic, or social harm) not previously recognized.

Noncompliance – a failure to follow applicable human subject protection regulations and/or IRB Policies or determinations. (see IRB Policy 130 “Discovery, Reporting and Investigation of Noncompliance”)

- Serious Noncompliance – noncompliance that adversely affects the rights, welfare or safety of participants or places participant at a greater risk of harm. An action or omission taken by an Investigator that a reasonable Investigator would have foreseen as placing a subject at risk of significant harm.
- Continuing Noncompliance – repeated actions or omissions that indicate an unwillingness to comply taken by an investigator that a reasonable investigator would have foreseen as compromising the scientific integrity of a study such that important conclusions can no longer occur.

PROCEDURE:

1. Upon discovery of an event, incident, experience, or outcome (referred to as “event” from this point forward) the PI or clinical designee completes the **Unanticipated Problem Worksheet**. The purpose of the UP Worksheet is to document the event and assess the significance to subject’s rights, welfare, safety and on the soundness of the research plan.
2. The **Unanticipated Problem Worksheet** contains the following:
 - Date of discovery
 - Date of report
 - Date of event
 - UP Category (Breach of Confidentiality, Protocol Deviation, Noncompliance)
 - Detailed description of the event
 - Explanation of how the event occurred based on a root cause analysis
 - Number of times this type or similar event occurred with explanation as to why previous corrective action did not prevent a recurrence

- Corrective Action plan to implement, improve or correct a system/process to prevent the event from recurring.
 - Risk Assessment with supporting rationale to determine:
 - if the event is unexpected, related or possibly related to the research **AND**
 - **significantly impacts** the soundness of the research plan or suggests the research placed participants or others at a greater risk of harm (physical, psychological, economic, or social harm) not previously recognized
3. **Events that do not rise to the level of having a significant impact** on participant's rights, welfare or safety or the soundness of the research plan, as determined by a clinical member of the research team, are reported to the Institute or Department QA Monitor or Research Manager using the completed UP worksheet form for review and are **reported to the IRB at time of continuing renewal** by placement on the UP cumulative report log. The Institute or Department QA Monitor or Research Manager reviews the UP worksheet to confirm risk assessment and if a determination is made, after discussion with the investigator, the event rises to the level of significance it will be submitted to the IRB. The review also assesses the adequacy of the corrective actions plans, trends in events and need for education, tools, or resources.
 4. Events that rise to the level of having a **significant impact** on participant's rights, welfare or safety or the soundness of the research plan are **reported within 10 working days from discovery/awareness to the IRB** using the completed UP worksheet form. The UP worksheet form should also be submitted to the Institute or Department QA Monitor or Research Manager.
 5. The IRB staff (designated by the IRB Chair and Executive Director) will initially assess all submitted UP Worksheets to assess whether the event rises to the level of a UP involving risk. Actions to be taken by reviewer include:
 - Contact the PI to obtain additional information on the event
 - Refer the event to the convened IRB
 - Determine the event did not meet the definition of an unanticipated problem involving risk. Return the report to the PI stating the event did not rise to the level of having a significant impact on participant's rights, welfare or safety or the soundness of the research plan. Inform the convened IRB of this action in an Activities Report.
 6. The convened IRB reviews reports of unanticipated problems involving more than minimal risk to participants or others to determine if the event meets the three criteria for a UP involving risk. The primary reviewer and the other IRB members receive copies of the UP Report submitted by the PI to review. Actions which may be taken by the convened IRB include:
 - a. No action due to a determination the UP event did not involve increased risk of harm to participants or others and the research may continue as designed;
 - b. Request additional information from investigator or through an IRB inspection;
 - c. Modification of the research protocol to minimize risks to participants;

- d. Notification of current participants when such information may relate to participants' willingness to continue to take part in the research
 - e. Modification of the continuing review schedule;
 - f. Modification to the consent process/document requiring reconsenting of participants;
 - g. Monitoring of the research;
 - h. Monitoring of the consent process;
 - i. Suspension or Termination of the study; IRB Policy #135; "Administrative Hold, Suspension, or Termination of IRB Approval" addresses notification to Investigators, Institutional Official, and Regulatory Agencies
7. The IRB will notify the Investigator immediately by phone or email if the convened IRB determines the study needs to be suspended or terminated. The IRB is required to notify appropriate institutional officials and federal authorities, including OHRP when the research is covered by DHHS regulations and FDA when the research is FDA-regulated, within 14 days when a determination is made that the event is an unanticipated problem involving increased risks to participants or others. The IRB Executive Director and the IRB Chair will complete a report for appropriate institutional officials and federal authorities that include the title of the research, name of the PI, any applicable federal award, a detailed description of the event, the corrective action and the actions of the IRB.
 8. The IRB will assess if the Unanticipated Problem was related to the absence or unclear IRB policy which would require the creation of a new IRB policy or modification to an existing IRB policy.
 9. The IRB shall review all events reported on the UP Cumulative Log at the time of study renewal to assess whether events are recurring and if corrective action plans are effective. (See IRB Policy 30 "Continuing Review"). The IRB shall also review if there is non-compliance to applicable human subject protection regulations and/or IRB policies. (See IRB Policy 130 "Discovery, Reporting and Investigation of Noncompliance")

Revised: 05/01/02, 10/23/02, 10/14/03, 6/10/04, 1/12/05, 6/29/05, 8/8/05, 5/30/06, 6/14/06, 6/3/2009, 1/20/10, 1/27/12, 3/26/13, 8/27/14

Event Reporting – Unanticipated Problems, Adverse Events, and Protocol Deviations

Policy

Federal regulations [45 CFR 46.103\(b\)\(5\)\(i\)](#) require IRBs to have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the federal department or agency head of any unanticipated problems involving risks to subjects or others. The IRB complies with all applicable local, state, and federal regulations in the conduct of human research studies. In keeping with these regulations, investigators are required to promptly report any unanticipated problem, adverse event or protocol deviation, with special attention to deviations involving risks to subjects or others. The IRB reviews the reports and fulfills all applicable reporting requirements to the appropriate institutional officials and federal departments or agencies.

The IRB has the authority to suspend or terminate a protocol that has been associated with unexpected serious harm to subjects or others.

Definitions

Unanticipated Problem is a problem that could adversely affect the rights, safety or welfare of the subjects, or others (e.g., family members, by-standers, and researcher/team) or which significantly impacts the integrity of research data. An example would be a breach of confidentiality or unintentional destruction of study records. CWRU and OHRP consider *unanticipated problems*, in general, to include any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Event

1. Any unintended negative experience associated with the study materials or research procedures.

2. Adverse events include both physical and psychological harms; although they most commonly occur in the context of biomedical research, they also can occur in the context of social and behavioral research.

Protocol Deviation is any alteration/modification to the IRB-approved protocol, whether intentional or inadvertent, that is not approved by the IRB prior to its initiation or implementation.

Minor Protocol Deviation is an incident involving noncompliance with the protocol but one that typically does not have a significant effect on the subject's rights, safety, welfare, or on the integrity of the resultant data.

Major Protocol Deviation is a more serious incident involving noncompliance with the protocol usually involving critical study parameters. Major protocol deviations generally affect the subject's rights, safety, or welfare, or the integrity of the study data.

Protocol Exception is a temporary deviation from the protocol that has been approved by the IRB before its initiation. Protocol exceptions are usually for a specific participant (e.g., allowing enrollment of a participant who is close to, but outside of, the age eligibility).

Minimal Risk means that both the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests ([45 CFR 46.102 \(i\)](#)).

Serious Adverse Events are adverse events that result in any of the following outcomes: death; a life threatening experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect. In addition, events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

Non-Serious Adverse Event is any event that causes interference with routine daily activities without major discomfort and these interferences do not persist. Non-serious events also include events that are easily tolerated and do not affect participation in routine daily activities.

Unanticipated Problems

There are types of incidents, experiences, and outcomes that occur that represent unanticipated problems, but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems that are not adverse events may also place others at increased risk of harm, but no harm occurs to the participant.

The primary responsibility for the evaluation of unanticipated problems lies with the investigator of the protocol. This includes the documentation, investigation, and follow-up of these events. For those events that require reports to the IRB it is the investigator's responsibility to submit the reports within three (3) business days of discovery of the problem or event.

If an incident, experience, or outcome meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The investigator must complete the Unanticipated Problems, Deviations, Adverse Events Form via iRIS. Failure to report an unanticipated problem in a timely manner may be considered a compliance matter and referred to the IRB for review and a compliance determination. If the Unanticipated Problem does not meet these criteria, then the event does not meet reporting criteria and should be retained in the investigator's file for reference.

All unanticipated problems involving risks to subjects or others must be reported to the IRB within three (3) business days of discovery of the problem or event. The following are examples of events that need to be reported by the investigator to the IRB as soon as possible, but within three (3) business days of the investigator learning of the event:

1. Information that indicates a change to the risks or potential benefits of the research.
2. A breach of confidentiality including inappropriate disclosure, lost or stolen confidential information.
3. Changes to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
4. Incarceration of a participant in a protocol not approved to enroll prisoners.
5. A woman becoming pregnant and inclusion of pregnant women.
6. Event that requires prompt reporting such as disqualification or suspension of investigator.
7. Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
8. Protocol deviation (including accidental or intentional protocol deviation) that caused harm to participants or others or indicates participants or others are at increased risk of harm.

Adverse Events

An adverse event is any unintended negative experience associated with the study materials or research procedures. The primary responsibility for the evaluation of these events lies with the investigator of the protocol. This includes the documentation, investigation, and follow-up of these events. For those events that require reports to the IRB, it is the investigator's responsibility to submit the reports in a timely manner. If new risks to the participants are identified they must be included in a revised consent form.

Adverse events are reported by using the *Unanticipated Problems, Deviations, Adverse Events Form* in iRIS. The form must be completely filled out and include any supporting documentation. iRIS automatically time stamps the submission. Reporting an event to the IRB does not relieve the investigator of the obligation to report the event to other agencies or university offices.

Multiple factors determine if an *Unanticipated Problems, Deviations, Adverse Events Form* is required. One of the most important distinctions is whether the event is expected or unexpected. To make this determination, it is necessary to know the underlying condition of the subject including co-morbidities, and the severity and frequency of events in participants who qualify for the study. An expected adverse event meets one or more of the following criteria:

- Attributed to the underlying condition of the participant being studied.
- Attributed to the subject population being studied.
- Identified in the literature, investigator brochure, other risk documentation or informed consent.

An unexpected adverse event meets one or more of the following criteria:

- Not listed in the informed consent, protocol, or other study documents.
- Not attributed to the underlying condition of the subject taking into account co-morbid conditions.
- Not attributed to the subject population
- Severity and/or frequency of the event are beyond the range previously known.

For all reporting periods "days" refers to business days after the investigator learned of the event. All reportable events need to be reported to the IRB within the timeline even if the information about the event is incomplete. Further information can be added with a follow-up report.

An example of an adverse event that would need to be reported includes a participant experiencing an unexpected amount of anxiety while completing a research questionnaire.

All adverse events, including those reported to a CWRU investigator must be promptly reviewed by the investigator and any event that changes the risk/benefit ratio of the study, or requires a change in the protocol or the consent form, must be reported to the IRB within 3 business days.

The investigator must make the protocol changes as soon as possible and submit the revised documents to the IRB via the Amendment form in iRIS.

Other events are reported as follows:

- All fatal events must be reported to the IRB as soon as the investigator learns of the event, if the investigator believes the event to be related to the study. If the death is determined to be unrelated to the study, it must be reported at the time of next Continuing Review.
 - Deaths which occur after the subject's research participation has ended do not need to be reported to the IRB unless the death is related to study participation.
- All serious adverse events must be reported as soon as the investigator learns of the event.
- All non-serious events and summary reports are kept in the investigator's files and do not need to be reported to the IRB. The IRB does not require the investigator to report adverse events that occur to subjects enrolled in an observational study or non-interventional study unless the event is related to study participation, causes a change in study design or increases risk for other participants.
- If a CWRU investigator is notified about an event that occurred at another site in a study related to, but not the same as, the CWRU protocol, and the event results in a change in the protocol, consent form, or the risk/benefit ratio, the adverse event must be reported within 3 business days of learning of the event.
- If the change in the CWRU protocol is due to publication of results from another study which has an adverse impact on the CWRU protocol, it should be reported as soon as the investigator learns of the valid publication.
- The investigator who conducts research projects funded by a federal agency is obligated to report adverse events that are serious and unanticipated simultaneously to both the federal agency and to the IRB. The IRB has a separate and distinct obligation to report the adverse events to government authorities

If the event changes the risk for other study participants and requires changes in the consent documents, report as soon as the investigator learns of the event (but within 3 business days).

Adverse events which occur in another study (including fatal events) and which do not result in a change in the protocol, consent form, or the risk/benefit ratio for the study, do not need to be reported to the IRB but should be kept on file by the investigator.

Reporting of Adverse Events at Continuing Review

Adverse events that do not result in a change in the protocol, consent form, or the risk/benefit ratio are reported to the IRB at the time of submission of the next continuing review or study closure. The continuing review form in iRIS requests a summary of all adverse events occurring since the last IRB review. This includes both events individually reported to the IRB since the last IRB review and events that do not need to be reported to the IRB until the continuing review.

Uploaded copies of the adverse event report forms need not be submitted with the continuing review because those forms remain in iRIS.

The investigator should provide an assessment of whether the adverse events present any additional risks to study participants. Any additional risks to participants must be included in a revised study application and revised informed consent forms that are reviewed and approved by the IRB.

Reporting of Adverse Events at Study Closure

If a participant has an adverse event after completing all of his or her study activities, and the study remains open at CWRU for other participants, the adverse event is only reported if it was study related.

Failure to Report Adverse Events

Failure to report an adverse event in a timely manner may constitute non-compliance and will be referred to the IRB for review as possible non-compliance, which will be processed as described in the CWRU IRB Non-Compliance policy.

IRB Review of Adverse Events and Unanticipated Problems

All adverse event or unanticipated problem reports are initially reviewed by the Chair or a Vice-Chair of the IRB before submitted to the full board to determine whether the problem is an unanticipated problem involving risks to participants or others based on whether the problem is:

1. Unexpected (in terms of nature, severity, or frequency) given:
 - a. The research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
 - b. The characteristics of the subject population being studied; and
2. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
3. Related (or probably/possibly related) to the study procedures/interventions.

If the IRB Chair or Vice Chair determines that the problem is NOT an unanticipated problem involving risks to participants or others, it will be reported to the IRB in the monthly notice to committee report.

If the IRB Chair or Vice Chair determines that the problem IS an unanticipated problem involving risks to participants or others, the problem is reviewed by a convened IRB as described below.

All unanticipated problems reviewed at full Board will be assigned a primary and secondary reviewer. The reviewers will usually be the Chair and Vice Chair; however another IRB member may also be assigned to review. If possible, the information about the event will be distributed

with the meeting packets; however, if time does not allow it, it will be distributed in advance to the primary and secondary reviewers and to the other Board members at the meeting.

The primary and secondary reviewers and the rest of the full IRB will receive completed *Unanticipated Problems, Deviations, Adverse Events Form* and any other related document deemed necessary. The complete IRB file is available to all members via iRIS before, during and after the IRB meeting.

When unanticipated problems are reviewed at an IRB meeting and determined by the Board to be an unanticipated problem, the IRB will consider whether any corrective actions or substantive changes to the research are required. At its discretion the IRB may request outside consultation to assist in its review. The IRB may consider any of the following and determine that corrective actions or substantive changes are required.

- Review changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects.
- Request further information from the investigator.
- Request modification of inclusion or exclusion criteria to mitigate the newly identified risks.
- Implementation additional procedures for monitoring subjects such as additional monitoring by an independent monitor.
- Suspension of enrollment of new subjects.
- Suspension of research procedures in currently enrolled subjects.
- Modification of informed consent documents to include a description of newly recognized risks.
- Require notification of additional information about newly recognized risks to current and previously enrolled subjects.
- Increase the frequency of continuing review.
- Halt new enrollment in the study pending a revised approved consent form and require currently active participants to be re-consented using the revised consent form.
- Referral to other organizational entities.
- Terminate all study activities.
- Accept the report with no changes to the risk/benefit ratio or the informed consent documents.

The minutes must document the IRB's discussion, determinations and actions. This includes but is not limited to:

- Whether the report is determined to be an unanticipated problem.
- Whether the study is to continue as written and approved.
- Whether the protocol and/or consent form needs to be revised to address any additional risks.
- Whether participants need to be re-consented.
- Whether additional information about the event needs to be provided.

- Whether the protocol is to be suspended or terminated.

The IRB will communicate its determination and finding to the responsible investigator by sending a letter outlining the findings of the IRB and any required actions of the responsible investigator. The IRB Office will report any event that has to be reported to Regulatory Agencies, Department Heads and Institutional Officials.

Protocol Deviations

An investigator with an IRB-approved protocol must conduct the protocol under the terms and specifications of the study as approved by the IRB. An investigator may not deviate from the approved procedures without prior IRB authorization except to avoid an immediate apparent hazard to subjects. Protocol Deviations must be reported by the investigator to the IRB within three (3) business days.

All protocol deviations are initially reviewed by the IRB Office. Deviations that result in harm to the subject are presented at a convened Board meeting and reviewed.

Deviations are reported using the *Unanticipated Problems, Deviations, Adverse Events Form* via iRIS. The investigator should explain the corrective actions taken to avoid future deviations. Protocol deviations that result in a change in the protocol, consent form or the risk/benefit ratio for the study should be reported to the IRB within 3 business days and an *Amendment Form* must be completed and submitted via iRIS. The Responsible Investigator must be sure to upload and attach the amended application protocol, consent form, along with other revised study documents.

Failure to report a protocol deviation in a timely manner may constitute non-compliance and will be referred to the IRB for review as possible non-compliance, which will be processed as described in the CWRU IRB Non-Compliance policy.

Examples of Deviations

- Informed consent obtained by someone not approved to obtain consent for the protocol.
- Use of invalid consent form, e.g., consent form without IRB approval; or outdated/expired consent form.
- Enrollment of a participant who was ineligible for the study.
- Performing a research procedure not in the approved protocol.
- Study medication dispensing or dosing error.
- Use of recruitment procedures that have not been approved by the IRB.
- Enrolling significantly more subjects than proposed in the IRB protocol.
- Failure to follow the approved study protocol that does not affect participant safety.(e.g., study procedure conducted out of sequence, failure to perform a required test, missing laboratory results, study visit conducted outside of required timeframe.)

References or Regulatory Citations[45 CFR 46.111](#)[45 CFR 46.103](#)[NIH Guidelines on Reporting Adverse Events to Institutional Review Boards, June 11, 1999](#)[OHRP Guidance on Reporting Incidents to OHRP, May 27, 2005](#)[OHRP Guidance January 15, 2007 - Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events](#)

**Case Comprehensive Cancer Center
Standard Operation Procedures for Clinical Research**

Title: Protocol Review and Monitoring Committee Accrual Monitoring
SOP #: PRMC-10.3.0
Version #: 4.0

Original Approval Date:	October 4, 2011
Effective Date:	November 4, 2011
Revision Dates:	November 12, 2012 April 7, 2015 June 21, 2017 April 20, 2020

1.0 Standard Operating Procedure Statement / Purpose / Background

A procedure documenting the process for accrual monitoring by the Protocol Review and Monitoring Committee (PRMC).

2.0 Scope

The PRMC is responsible for monitoring accrual to interventional clinical trials and mandating closure of studies when low accrual affects the likelihood of successful and timely completion of the research.

3.0 Responsibility

PRMC, Case CCC Clinical Research Leadership Committee, Principal Investigator (PI), Clinical Trials Units (CTU)

4.0 Definitions

4.1 Case CCC: Case Comprehensive Cancer Center.

4.2 OnCore® Clinical Trials Management System (referred to as OnCore): database to track information from clinical trials conducted by the Case CCC.

4.3 NCI: National Cancer Institute

4.4 UH: University Hospitals

4.5 CC: Cleveland Clinic

5.0 Procedure

5.1 Reports will be run monthly to review accrual to trials. Accrual to interventional trials is reviewed every 6 months from study activation. Accrual to sponsored trials that have not accrued at least 1 patient in the previous 6 months will be reviewed. Investigator-initiated trials that have not accrued 50% of expected 6-month accrual will be reviewed.

5.1.1 For sponsored joint trials (between UH and CC) whereas the open to accrual date is different, each site will be reviewed separately. Communication between the sites must occur if one side chooses to close voluntarily. If the PRMC decides the study should be closed at a particular site, the CTU must communicate with the other site so regulatory processes can be put in place.

5.1.2 For investigator initiated trials joint (between UH and CC) the PRMC will monitor from the earliest open date. Decisions will be sent to the

**Case Comprehensive Cancer Center
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lead site and cc the non-lead site. Any decision made on closure should be communicated with the non-lead site by the CTU and PRMC.

5.1.3 Accrual analysis conducted by PRMC will utilize OnCore for patient enrollment information.

5.1.4 Rare Disease Trials: NCI guidelines regarding rare disease states that the PRMC can make exceptions for trials that fall under the definition of rare disease, this includes all pediatric trials. Adult rare disease studies will be monitored yearly and pediatric studies will be monitored every 2 years from activation.

5.2 The PRMC will send a memo to the designated clinical site CTU representative. This document will contain the current status and accrual information. Response to questions as well as a justification of the accrual level, a corrective strategy to improve accrual, or voluntarily closing the study is required.

5.3 CTU representative is responsible for acquiring the response from both the CTU and PI. These responses will follow discussion between the PI and CTU. Completed memo is sent back to PRMC within 2 weeks.

5.4 PRMC will review the responses at the following PRMC meeting. Based on the response, the PRMC will recommend closure or continuation to further accrual.

5.4.1 Decision to continue will be documented and sent to the CTU representative and PI.

5.4.2 Trials recommended by PRMC to close will receive a second closure memo addressed to the PI and “cc” the CTU representatives and Case CCC Clinical Research Leadership Committee. If the PI wishes to appeal the trial closure decision, a letter of explanation should be sent to the Case CCC Clinical Research Leadership Committee via the PRMC manager within 1 week of closure notification. The Case CCC Associate Director for Clinical Research will respond in writing of the decision regarding trial closure. This decision will be final.

6.0 References

■ PRMC website: <https://case.edu/cancer/research/clinical-research-office/prmc>

7.0 Appendices: None.

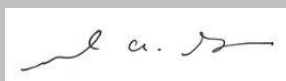
SOP #: PRMC-10.3.0; Version #: 4.0

Approved by:

Name: Mikkael Sekeres, MD

Position: Deputy Associate Director of Clinical Research; Director of Clinical Trials

Signature:



Date: 4/20/2020

Appendix I

Monitoring Training Checklist

This checklist with appropriate documentation will be maintained in departmental files. The designated management personnel will verify that the information on this form is complete and that the staff is prepared to monitor.

Name of Monitor: _____

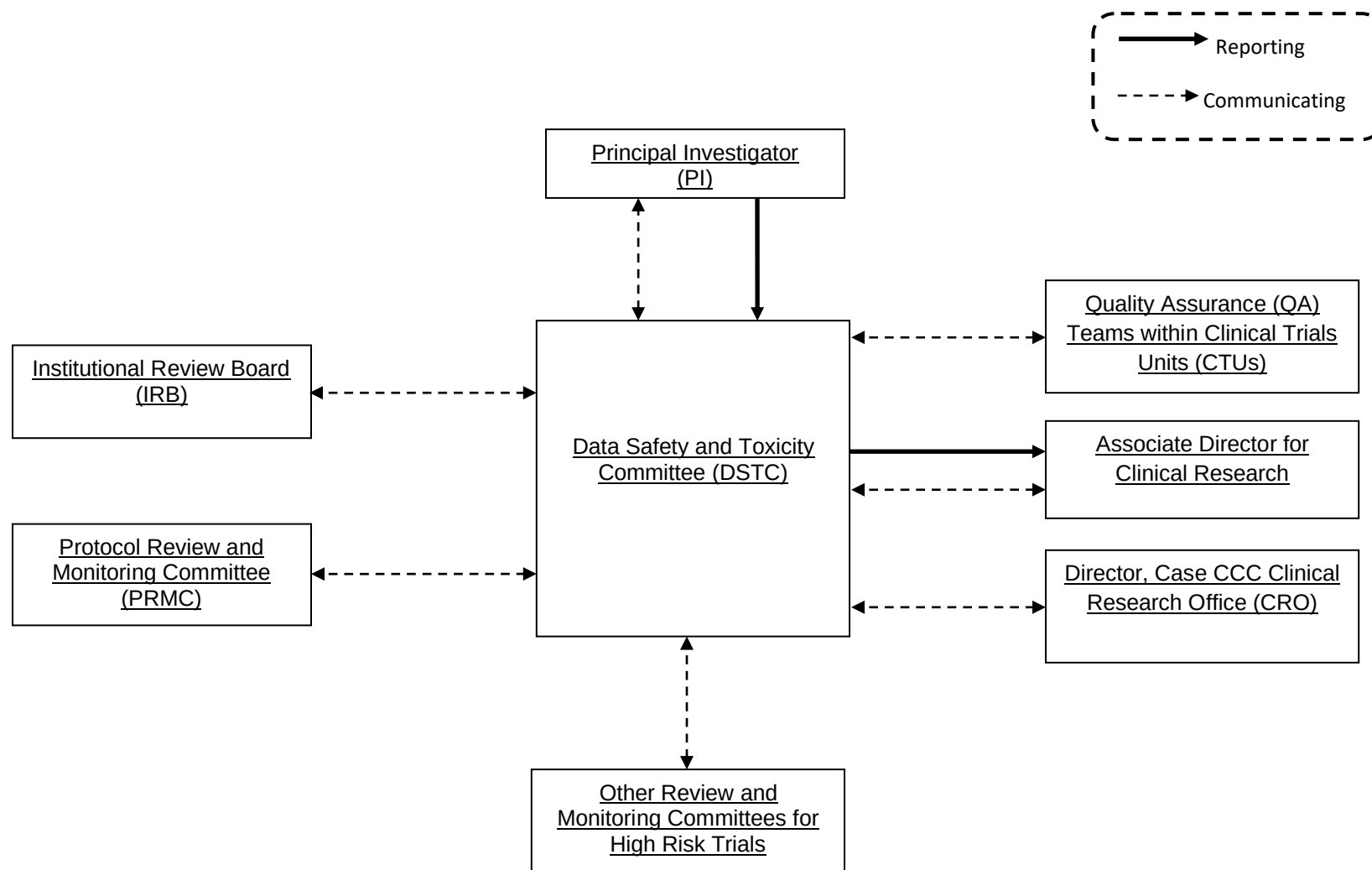
Date of Hire: _____

Requirements	
Document Name	Yes or No
Current Curriculum Vitae that demonstrates two or more years of clinical research experience	
Copy of quality assurance course (including certificate of completion, agenda) on file	
Documentation of at least two site monitoring training visits with a trained and more experienced site monitor or minimum of six months hands-on monitoring experience/assessment of regulatory compliance	
Review of Institutional Policy	
Review of CCCC Monitoring of Clinical Investigations SOP	
Review of CCCC Clinical Trials Manual of Operations	
Review of ICH E6 Good Clinical Practice Guidelines	
Review of Federal Code of Regulations Title 21 Part 11, 50, 54, 56, 312, 812 Guidelines for Monitoring of Clinical Investigations (January 1988)	

Monitor Signature: _____ **Date:** _____

APPENDIX D

Case Comprehensive Cancer Center Data and Safety Monitoring Plan Reporting Summary (October 2016)



APPENDIX E

Case Comprehensive Cancer Center: Protocol Review and Monitoring Committee Roster (July 2020)		
Faculty		
Name	Academic Rank	Expertise
Leland Metheny, MD (Chair)	Assistant Professor	Adult Hematology/Oncology
Shilpa Gupta, MD (Co-Chair)	Associate Professor	Adult Hematology/Oncology
Bruno, Debora, MD	Assistant Professor	Adult Hematology/Oncology
Choi, Sera, MD	Assistant Professor	Adult Hematology/Oncology
Cullen, Jennifer, PhD	Associate Professor	Population and Quantitative Health Sciences
Fu, Pingfu, PhD	Associate Professor	Population and Quantitative Health Sciences
Gallogly, Molly, MD	Assistant Professor	Adult Hematology/Oncology
Hurley, Karen, PhD	Assistant Professor	Neurologic Institute
Jagadeesh, Deepa, MD	Assistant Professor	Adult Hematology/Oncology
Mahdi, Haider, MD	Assistant Professor	Adult Hematology/Oncology
Malek, Ehsan, MD	Assistant Professor	Adult Hematology/Oncology
Mansur, David, MD	Associate Professor	Adult Hematology/Oncology
Nazha, Aziz, PhD	Assistant Professor	Adult Hematology/Oncology
Pink, John, PhD	Assistant Professor	Cancer Biology, Drug Development
Selfridge, Jennifer Eva, MD	Assistant Professor	Adult Hematology/Oncology
Shepard, Dale, MD, PhD	Assistant Professor	Adult Hematology/Oncology
Tomlinson, Benjamin, MD	Assistant Professor	
Trapl, Erika, PhD	Associate Professor	Population and Quantitative Health Sciences
Tatsuoka, Curtis, PhD	Associate Professor	Population and Quantitative Health Sciences
VanHeyst, Kristen, DO	Assistant Professor	Adult Hematology/Oncology
Vargas, Roberto, MD	Assistant Professor	Adult Hematology/Oncology
Staff		
Name	Role	Expertise
Bogati, Samjhana, RN	Research Nurse	Nursing
Hanigosky, Barbara, RN	Research Nurse	Nursing
Wood, Laura, RN	Research Nurse	Nursing
Jia, Sophia, MS	Biostatistics	Biostatistics
Margevicius, Seunghee, PhD	Biostatistics	Biostatistics
Moizuk, Shaun, RPh	Pharmacist	Investigational Drug Services
Nottingham, Megan, RPh	Pharmacist	Investigational Drug Services
Porter, Amy, RPh	Pharmacist	Investigational Drug Services
Thomas, Jenna, RPh	Pharmacist	Investigational Drug Services

Cudak, Gail	Patient Advocate	Patient and Community Perspective
Morton, Barbara	Patient Advocate	Patient and Community Perspective
Wilson, John	Patient Advocate	Patient and Community Perspective
Firstencel, April, BA	PRMC Manager	PRMC Manager and Coordinator
Kevin Hoy, PhD (alternate for April Firstencel)	Administrative Director, Case CCC Clinical Research Office	Administrative Director, Case CCC Clinical Research Office

APPENDIX F

Case Comprehensive Cancer Center Data Safety and Toxicity Committee Roster (August 2020)		
Faculty		
Name	Academic Rank	Expertise
Advani, Anjali, MD (Chair)	Associate Professor	Adult Hematology/Oncology
Caimi, Paolo, MD (Co-Chair)	Assistant Professor	Adult Hematology/Oncology
Li, Ming PhD	Assistant Proffessor	Bioinformatics & Biostatistics
Geiger, Jessica	Associate Staff	Adult Hematology/ Oncology
Bajor, David	Professor	Adult Hematology/Oncology
Stephans, Kevin, MD	Associate Staff	Radiation Oncology
Staff		
Name	Role	Expertise
Collins, Emily	QA Supervisor	Quality Assurance
Kane, Donna	Nurse	Nursing
Riendeau, John	Nurse	Nursing
Morey, Keralee	DSTC Coordinator (Cleveland Clinic TCI)	DSTC Coordinator; Research Regulatory & QA Coordinator
Pasca, Simona, CCRP	DSTC Coordinator (Case CCC & UH SCC); Quality Assurance Specialist	DSTC Coordinator; Quality Assurance
Rump, Matt, CCRP	Research Database Manager Non-voting	Information Technology
Bogati, Samjhana	Nurse	Nursing