



# **University of Florida Health Cancer Center**

## **Data and Safety Monitoring Plan**

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## Manual Updates

Version 1.0 is NEW

### Frequently Used Abbreviations

ADCI	Associate Director for Clinical Investigation
AE	Adverse event
CAPA	Correction Action and Preventative Action
COI	Conflict of interest
CRO	Clinical Research Office
DISC	Data Integrity and Safety Committee
DSG	Disease Site Group
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
ETCTN	Experimental Therapeutics Clinical Trials Network
FDA	Food and Drug Administration
FG	Feasibility Group
GCP	Good Clinical Practice
IIT	Investigator initiated trial
IND	Investigational new drug
IRB	Institutional review board
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NIH	National Institutes of Health
PI	Principal investigator
SAE	Serious adverse event
SIV	Site initiation visit
SOP	Standard operating procedure
SRMC	Scientific Review and Monitoring Committee
UF	University of Florida
UFHCC	University of Florida Health Cancer Center
UP	Unanticipated Problem

## OVERVIEW

This document describes the components and operating procedures that govern data and safety monitoring of University of Florida Health Cancer Center (UFHCC) clinical trials. The goals of the institutional data and safety monitoring plan (DSMP) are to ensure the safety of participants, the validity of data, and to conduct appropriate monitoring and termination of studies in the event that undue risks are identified. All clinical trial protocols must have a protocol-specific DSMP which is reviewed and approved by the UFHCC Scientific Review and Monitoring Committee (SRMC). The scope of data and safety monitoring depends on the phase and complexity of the study and may be performed by the principal investigator (PI) alone or in conjunction with an independent data and safety monitoring board (DSMB). Regardless of the method used, monitoring must be performed on a routine basis and commensurate with trial risk.

This plan covers all phases of interventional clinical trials and, particularly, investigator-initiated clinical trials for which there is no independent extramural monitoring program. At the UFHCC, the responsibility for data and safety monitoring primarily rests with the PIs and the Data Integrity and Safety Committee (DISC).

### 1.0 INTRODUCTION

The UFHCC maintains a diverse research portfolio including investigational treatment, supportive care, prevention, diagnostic and screening trials. The UFHCC is committed to ensuring the safety of research subjects enrolled on these clinical trials, adherence to good clinical practice (GCP), and generation of high-quality data. This is achieved through the integrated efforts of various core committees and groups that comprise the UFHCC Research Oversight System. The Research Oversight System represents the integrated components of the UFHCC Protocol Monitoring and Review System and Clinical Protocol and Data Management systems.

This plan applies to research conducted by the UFHCC members or University of Florida (UF) faculty conducting cancer-relevant clinical research throughout UF including the conduct of UF investigator-initiated trials (IITs) performed at UFHCC Academic Research Consortium sites.

This DSMP has been written in accordance with the National Institutes of Health (NIH) policies for data and safety monitoring and documents the plan established by the UFHCC for the oversight of cancer-relevant clinical trials conducted by UF investigators.

This plan addresses:

- monitoring of patient safety,
- reporting of adverse events (AEs), unanticipated problems (UPs), and deviations,
- assessing study progress,
- reviewing data integrity and accuracy,
- overseeing compliance with the protocol, the International Conference on Harmonisation (ICH) GCP, and all applicable regulatory requirements (e.g., institutional review board [IRB], Food and Drug Administration [FDA]).

### 2.0 SCOPE OF APPLICATION

#### 2.1 Definition of a Clinical Trial

The National Cancer Institute (NCI), defines a clinical trial as “*a prospective study involving human subjects designed to answer specific questions about the effects or impact of a particular biomedical or behavioral intervention; these may include drugs, treatments, devices, or behavioral or nutritional strategies.*” Trial participants may include current or former cancer patients, persons without cancer who may be at risk for developing cancer, or healthy controls enrolled in cancer-relevant studies.

Studies that include nutritional, behavioral, and psychosocial interventions are considered to be clinical trials as are those evaluating diagnostics (such as imaging, etc.) in which findings alter the patient’s clinical care. The NCI further defines the following behavioral and diagnostic studies as clinical trials:

- “*Molecular or imaging diagnostics - a study is considered to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. In this way, the information from the diagnostic may have an impact on some aspect of*

*outcome, and assessment of this impact may be a key goal of the trial. By contrast, studies that do not use information from the diagnostic test in any manner that can affect the outcome of study subjects, but whose objective is only the gathering of data on the characteristics of a new diagnostic approach, are not clinical trials and are not covered by this data and safety monitoring plan, unless performing the diagnostic test itself imposes some risk on study subjects.”*

- *“Behavioral clinical trials - interventions whose goals are to increase behaviors (e.g. cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life (e.g., among cancer survivors) and reduce the negative sequelae of treatment. Interventions may pertain to cancer prevention, early detection, treatment, and survivorship. Observational studies and those that do not test interventions are not clinical trials.”*

Studies that are not considered clinical trials according to the NCI definition (observational studies, epidemiologic studies, studies of diagnostics that do not affect patient care, and studies that do not test interventions) are not subject to routine monitoring by the UFHCC Research Oversight System unless performing the diagnostic test itself imposes some risk on study subjects.

## **2.2 Auditing & Monitoring**

Auditing and monitoring are two major components of the Research Oversight System and serve to ensure that investigators and study teams are maintaining high-quality protocol management and data integrity practices. Every study meeting the definition of a clinical trial must have an adequate plan for assessing subject safety, event monitoring, and routine review of data and study progress. The Research Oversight System provides varying levels of review depending on the existence of a protocol-specific or external DSMP, the risk level, and the complexity of each study. Studies with acceptable external DSMPs, including those conducted by the NCI’s National Clinical Trials Network (NCTN) or Experimental Therapeutics Clinical Trials Network (ETCTN), and studies that are sponsored by pharmaceutical companies with its own DSMB, do not require **routine monitoring** through this UFHCC DSMP.

Even if routine monitoring is not required to be conducted locally, the UFHCC DSMP addresses quality assurance measures that will be applied to **all cancer-relevant interventional clinical trials** conducted by the UFHCC.

This DSMP has been designed to specifically address trials conducted by sponsor-investigators (hereafter referred to as IITs). The FDA defines a sponsor-investigator as “an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.” For the purposes of this plan, this definition has been broadened to include any clinical trial that was initiated and conducted by an investigator. **UF IITs are further characterized as trials that both originated at UF and are centrally managed by the institution.** Trials subject to this plan may include those supported via externally peer-reviewed grants (NIH, NCI, or other agencies), foundation or sponsor grants or gifts, funding from pharmaceutical companies, or through internal funding mechanisms. UF IITs are required to satisfy the minimum requirements described in this DSMP. Multi-center IITs originating at an outside institution are required to incorporate a DSMP into their protocol or submit their DSMP for consideration to the SRMC. If the coordinating center does not have a plan, they will be required to comply with the plan outlined in this document in order to include UF as a participating site.

Auditing and monitoring activities are covered in more detail elsewhere in this DSMP.

## **3.0 CONFLICTS OF INTEREST**

UF notes that a conflict of interest (COI) may occur when a “person serves or represents two distinct entities, or persons, and must choose between two conflicting interests or loyalties.” The UFHCC strives to ensure that real or perceived COI do not compromise research integrity. COIs that are not properly disclosed and managed could negatively impact the investigator, institution, trial data, and, most importantly, subject safety.

COIs may include professional interest, proprietary interest, and miscellaneous interest, as described in the NIH Financial COI Guide [1] and UF’s COI and Outside Activities Policy document [2]. These documents outline rules and reporting requirements for conflicts (including financial conflicts and disclosures), and contain policies related to clinical research. UF uses a web-based system for reporting COI for institutional review and individual COI

information must be updated annually. Reported conflicts are reviewed by the faculty or staff member's respective department chairperson and the dean (or the director of the college or other unit, in which the faculty or staff member is employed). If a COI exists and is deemed by the faculty/staff leadership to be significant, the university will work with the employee to develop an adequate conflict management plan. UF IRBs will also review all disclosed COI and determine whether any additional safeguards are required.

In accordance with UF policy, all members of the DISC, SRMC, and CRO quality assurance staff must disclose any actual or potential conflicts of interest to the UFHCC Director and the UF Office of Research. Conflicts that arise during a member's tenure must also be disclosed and addressed. Individuals may not review trials that they are involved in as a PI, co-investigator, study team member, or consultant in any capacity. The conflicted individuals must recuse themselves from all closed discussions about the trial. In the event that recusal during DISC operations results in quorum no longer being met, the DISC Chair shall appoint an ad hoc member to review that protocol only.

In addition to the general guidelines related to COIs, UFHCC has established the following specific committee rules that are applicable to DISC members with conflicts:

- Committee members may not participate in voting on protocols for which they serve as a PI, co-investigator, or in any other study staff capacity. Committee members with trial responsibilities are required to leave the meeting during the discussion and the vote on the project. A PI may not serve as an auditor for his or her own trial.
- Any committee member who is not an investigator on a trial, but who has another identified conflict may or may not be allowed to vote on actions related to the protocol. This will be determined by the committee Chair and/or vice-Chair. Those individuals with significant conflict related to a trial will not be allowed to vote on items related to that trial, as described above.

#### **4.0 RESEARCH OVERSIGHT SYSTEM AND COMPONENT RESPONSIBILITIES**

The UFHCC has a systematic and organized process for the review and conduct of cancer-relevant clinical trials. This system supports multi-level reviews of all trials to ensure they receive appropriate consideration in the areas of clinical application, feasibility, and scientific merit as defined by the UFHCC. The committees and groups comprising UFHCC's Research Oversight System work together to provide complementary reviews that are non-overlapping, but each has a distinct and clearly defined role (**Appendix A**).

All cancer-relevant trials are brought forward by a UFHCC member PI to be initially vetted through and endorsed by one of UFHCC's Disease Site Groups (DSG) (**Appendix B**) prior to review by the SRMC. The role of SRMC is to confirm the scientific foundation of the proposed study, assure the proposed DSMP is appropriate based on the risk assessment, prioritize each study based on scientific merit, determine its alignment with UFHCC priorities (**Appendix C**), ensure there is an adequate number of patients to meet accrual requirements and monitoring scientific progress of the trial once activated. The DISC and the CRO quality assurance staff, in conjunction with the PIs and study teams, are responsible for data integrity and safety monitoring.

All Research Oversight System units, groups, and committees report to the UFHCC Associate Director of Clinical Investigation (ADCI), while the DISC additionally reports to the UFHCC Deputy Director who also serves as the DISC Chair. In this way, separate direct supervision and advocacy for the opening and conduct of clinical trials is distinct from the oversight of such trials. The responsibilities of these groups and committees that are related to data integrity and safety monitoring are described below. These components ensure adequate and continuous oversight of qualifying clinical trials conducted at the institution.

#### **4.1 Principal Investigator and Study Team**

##### **4.1.1 Principal Investigator Responsibilities**

The PI remains at the center of the Research Oversight System and is ultimately responsible for ensuring that a clinical trial is conducted in compliance with the protocol, the DSMP, and all relevant laws and regulations.

The PI must develop or otherwise ensure that a DSMP is incorporated into each interventional study protocol. Protocol-defined DSMPs are reviewed and approved by the SRMC and subsequently carried out by the PI, DISC, and/or other oversight bodies. The PI must also ensure that any future changes to an SRMC-approved plan are re-reviewed and approved by the SRMC.

The PI may delegate the authority to perform certain tasks to other study team members but must retain the responsibility for each of the tasks. The study team may be comprised of individuals including, but not limited to, investigators, research coordinators, clinical research assistants, and biostatisticians. Each study team should meet at regular intervals to ensure routine review of accruals, AEs, UPs, and overall study progress.

#### **4.1.2 Concept Refinement Support for Investigators**

To support investigators in the successful development and completion of UF-sponsored interventional IITs, concepts intending to be developed into protocols that utilize Clinical Research Office (CRO) resources undergo a centralized concept pre-review process. This resource is intended to ensure that concepts are placed on a path that maximizes activation and enrollment success while prioritizing the resources of the CRO and leveraging the collective experience of UFHCC leadership. This concept pre-review involves assessment of a proposal that includes the scientific background, description of the study intervention, statistical data analysis plan, institutional budget development, justification of personnel resources needed for the project, and documentation of support by the members of the DSG or research program. Such a submission may be in response to a UFHCC-directed call for concepts or through ad hoc investigator requests. The UFHCC ADCI through the UFHCC CRO approves concept submission to the SRMC upon verification of the above prerequisites.

#### **4.2 Disease Site Groups**

UFHCC members serving as clinical investigators are organized into DSGs. The UFHCC DSGs are the units whereby the clinical research portfolios are organized, managed, and executed. These DSGs are both disease specific (e.g., thoracic, breast, or gynecological) and disease agnostic (i.e., experimental therapeutics group or cancer population sciences). Each DSG is charged with developing and maintaining a portfolio of trials that brings forward scientific hypotheses developed in the UFHCC Research Programs, meets the needs of our patient population without unjustified competition or overlap, and successfully reaches the study goals. However, the final prioritization determination and oversight for all UFHCC clinical research is the responsibility of the SRMC.

The DSGs review all new and ongoing studies under their purview. All new interventional trials must be reviewed and approved by the applicable DSG prior to SRMC submission (for example, any clinical trials conducted in breast cancer must be vetted through the breast DSG). The sponsoring DSG research leader must attest to the projected annual accrual, allocation of UFHCC CRO resources, presence or absence of competing studies, and overall endorsement of support from the group. In addition, the DSG leaders are responsible for evaluating the impact of the proposed study on the patient population at UF Health and/or the UFHCC catchment area.

#### **4.3 Feasibility Group**

The UFHCC recognizes that a common barrier to successful trial completion is inadequate resource allocation. As a steward of limited resources, the UFHCC FG is responsible for reviewing the non-scientific aspects of a study being considered. The goal is to assist the PIs and DSGs in ensuring adequate institutional, financial, personnel, and patient resources are available before committing efforts towards trial activation. The UFHCC FG provides this information as a required component of UFHCC-supported (financial or other in-kind support) trials, UFHCC CRO-managed protocol development, and as a consultant to other UFHCC investigators. The FG issues a recommendation of feasible or non-feasible for each study reviewed to supplement DSG decision making. The FG is also involved in corrective action plan development for all studies at risk for closure or being placed on probation by the SRMC.

#### **4.4 Scientific Review and Monitoring Committee**

Upon endorsement by a DSG, SRMC reviews the scientific merit, methodology, validity of statistical analyses, adequacy of the protocol-specific DSMP, risk level, and scientific priority of appropriate studies. All cancer-relevant studies conducted at the UFHCC or supported with institutional resources must be reviewed and approved by the SRMC prior to study initiation. Cancer-relevant studies are those that include a known or suspected diagnosis of cancer as a part of eligibility criteria. For studies that may enroll cancer and non-cancer patients, review of the study is only required if the objective of the trial is to study cancer, cancer-related symptoms or risk factors, or if the PI only plans on enrolling current, former, or suspected cancer patients. Interventional studies, including those that involve treatment, supportive care, or diagnosis of cancer, that have

not received prior external peer review must undergo full committee review while non-interventional studies may qualify for expedited or administrative review. In addition, major amendments for all full-board studies must be submitted for review for the entire duration of the study's active accrual period. Trials that have received prior external peer review undergo DSG and expedited SRMC review in order to verify alignment with the UFHCC patient population, assess competition with ongoing studies, and determine the ability of the UFHCC to rapidly and efficiently accrue patients to such trials.

Consistent with the priorities established by the UFHCC Director, the UFHCC SRMC will ensure prioritization of studies and monitor all cancer-relevant studies for expected progress relating to accrual goals and performance standards (**Appendix C**). As documented in the SRMC Policies and Procedures Manual [3], the SRMC has the authority and charge to close any study failing to meet accrual goals and may require change or closure of trials that have become obsolete by new advances in the field and, therefore, whose scientific rationale has become superseded by changes in clinical practice.

The SRMC reviews the full protocol's proposed safety monitoring plan for completeness and adherence to the guidelines contained within this DSMP. SRMC will also assign a risk level for IITs that determines the minimum review frequency by the DISC (see **Section 5.1.1**). Risk level assignment is also confirmed by the DISC. Protocols without an adequate protocol-specific DSMP that cannot conform to UF's institutional DSMP will not be approved. After approval of a study and during ongoing progress review, the SRMC will notify the DISC of any changes to the protocol or changes in study status (e.g., suspension or closure to accrual) for those studies under DISC oversight. Similarly, DISC is responsible for informing SRMC of any findings that may impact the scientific merit of a trial.

In the event that SRMC becomes aware of misconduct or other issues impacting research integrity, the SRMC will contact all appropriate authorities (e.g., IRB, FDA, study sponsor, and DISC) and may take actions to suspend or close the study. In the event that a suspension or closure occurs on an NCI-funded trial, the SRMC will ensure the PI reports this to the appropriate NCI representative. SRMC membership and functions are distinct and separate from that of DISC.

#### **4.5 University of Florida Institutional Review Boards**

UF works with several IRBs that are responsible for the ethics review of all research that involves human subjects. UF primarily utilizes the three UF IRBs (IRB-01, 02, and 03) in addition to the Western IRB and the NCI Central IRB. UF IRB-01 may also cede review to other qualified IRBs as allowed per UF policy. IRB review focuses on study ethics and subject safety, and their assessment is separate, but complimentary, to the roles of the SRMC and DISC. The requirement for initial and ongoing ethics review of applicable studies applies regardless of the originator.

#### **4.6 Data Integrity and Safety Committee**

The DISC serves as the independent committee charged with review of interventional UF IITs that do not have an external SRMC-approved DSMB. The DISC concentrates on the review of safety, AEs, UPs, study endpoints, protocol compliance, and data integrity. NCTN, ETCTN, industry-sponsored, and other studies with an established SRMC approved DSMP/DSMB are not subject to DISC oversight (see **Section 6.0** for more information).

#### **4.7 Clinical Trials Quality Assurance**

The UFHCC CRO quality assurance staff works within the context of the Clinical Protocol and Data Management to implement all cancer trial auditing for the center. As previously stated, this function is independent of the continuous DSMP for a protocol. The team meets monthly and consists of members with expertise in clinical oncology, research operations, regulatory requirements, and quality assurance. Quality assurance staff provide information to DISC, but operate independent of them. Audit operations are overseen by the UFHCC Compliance Group (see **Section 7.0**).

Quality assurance staff provide auditing for all interventional trials conducted by the UFHCC, ranging from low-risk to complex, including IITs. Audits are conducted according to established review frequency and ad hoc as needed (see **Section 7.3**). Routine, random, and "For Cause" audits may also be conducted for any cancer-relevant study conducted at the UFHCC. All auditing activities are performed consistent with the ICH GCP

guidelines, which define auditing as a “systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and whether the data were recorded, analyzed and accurately reported according to the protocol, sponsor’s standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).” The UFHCC audit process is also intended to evaluate the effectiveness of current training, education, and monitoring practices. Findings may translate to modifications in SOPs, policies, or Research Oversight System activities.

Formal reports summarizing the findings of audits with identification of any specific findings warranting activation of Correction and Preventative Action (CAPA) plans are provided to the PI for review and response. Audit reports are also provided to the DISC, the ADCI, and the Administrative Director of the CRO. Quality assurance staff also coordinate external audits by sponsors or governmental agencies, such as Theradex, the NCTN Research Bases, external sponsors, and UF institutional audits including audits of protocols managed through the UFHCC Academic Research Consortium as required.

#### **4.8 Clinical Research Office Leadership**

<b>Table 1. UFHCC CRO Leadership</b>	
Alison Ivey, RN, MS, OCN, CCRP	Administrative Director, CRO
Leslie Pettiford, RN, MS, OCN, CCRC	Assistant Director, Study Coord & Data Mgmt
Alisha Daniels, MD, MHA, CCRC	Assistant Director, Project Mgmt & Reg Affairs
Ashley Anderson, MBA, ACRP-CP	Assist Director, Research Admin & Compliance
Robert Houlihan, DHA, MBA, FACHE, CCRP, CRA	Associate Director for Administration, UFHCC
Thomas George, MD, FACP	Associate Director for Clinical Investigation, UFHCC

The UFHCC CRO leadership team (**Table 1**) is comprised of experienced investigators and clinical research administrators that represent the key cross-functional units within the center. The leadership team members work collaboratively to monitor and develop processes and recommendations for improvements and innovations within the cancer research enterprise. The Research Oversight System (**Appendix A**), through the UFHCC CRO leadership team, executes the system established by the UFHCC Director.

#### **5.0 PROTOCOL MONITORING PLAN**

UFHCC requires that all institutionally sponsored IITs follow the guidelines outlined in the UFHCC DSMP. During the scientific review process for any new cancer-relevant clinical trial submission, the SRMC evaluates the proposed DSMP as outlined in the protocol. The UFHCC DSMP may also apply to other externally sponsored trials if they do not have an adequate plan in place. Trials that require DISC oversight will have a risk level assigned by the SRMC.

#### **5.1 Institutional Risk Assessment**

The SRMC has defined four risk levels that may be assigned to clinical trials. Risk level is defined based upon the nature of the intervention, the phase of the protocol, the risks of the intervention, and the complexity of the study. Each risk level specifies a minimum DISC monitoring frequency.

For institutional IITs and other clinical trials without an established data safety and monitoring plan, the SRMC will review the protocol and determine the appropriate level of monitoring required. The assigned level of risk will be reported back to the DISC and the study PI by the SRMC administrator and recorded in the Clinical Trials Management System (CTMS).

#### **5.1.1 Risk Assessment Levels**

The SRMC establishes the required level of monitoring for all studies under DISC oversight. This risk level will be determined based upon the protocol phase, objectives, study intervention, level of risk to subjects, and overall complexity. The assigned level of risk will be reported to the DISC and the study PI by the SRMC administrator. Note that all phase III studies (regardless of the level of risk – minimal vs greater than minimal risk) must be overseen by a DSMB.

Protocols will be classified by the SRMC into one of the following general categories of risk. Per 45 C.F.R. § 46.102(i), “Minimal risk means that 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.”

Level 1 – **Low risk** investigator initiated interventional trials. Examples include:

- Diagnostic or screening trials involving minimal risk procedures
- Trials involving accepted doses of over-the-counter drugs, or vitamins and supplements
- Behavioral or health services research (HSR) trials
- Trials involving diet or exercise involving minimal risk

Level 2 – **Moderate risk** investigator initiated or externally sponsored interventional (such as drug, biologic or device) trials using FDA approved or commercially available compounds or interventions. Examples include:

- IND exempt phase II and III trials
- Trials involving delivery of radiation therapy
- Screening, diagnostic, behavioral, HSR, diet or exercise trials that involve invasive or greater than minimal risk procedures or interventions that ordinarily would be regarded as minimal or low risk but are being tested in a context where the risk might be perceived as higher.

Level 3 – **High risk** investigator initiated or externally sponsored interventional trials (such as investigator-sponsored INDs, phase I trials, studies requiring biosafety approval, or other areas that may be designated by NIH as high risk). Examples include:

- UF investigator as IND/IDE holder
- Phase I drug, device, bone marrow transplant, cellular therapy, and surgical trials
- Any trial that requires UF biosafety committee approval
- UF multisite interventional trials

Level 4 – Complex trials involving **very high risk** to subjects and a high level of complexity such as first in human or gene transfer studies.

**Table 2** provides the DISC monitoring frequency and other details related to these risk levels assigned by the SRMC. Note, these DISC monitoring frequencies are minimum standards set uniformly by the center, but more stringent oversight may be specified in each protocol-specific DSMP.

<b>Table 2. Study Monitoring Frequency</b>				
<b>Risk Level</b>	<b>DISC Review And Monitoring</b>	<b>Regulatory Document And Informed Consent Content Review</b>	<b>Patient Case Review</b>	<b>Investigational Ancillary Services*</b>
Level 4	Quarterly	Quarterly	<b>1<sup>st</sup> Visit:</b> 100% of cases	Semi-Annual
			<b>F/U Visits:</b> 50% of cases <i>or</i> a minimum of 3 cases	
Level 3	Semi-Annual	Semi-Annual	<b>1<sup>st</sup> Visit:</b> 100% of cases up to 5 cases	Semi-Annual
			<b>F/U Visits:</b> 20% of cases <i>or</i> a minimum of 3 cases	
Level 2	Annual	Annual	<b>1<sup>st</sup> Visit:</b> 50% of cases up to 5 cases	Annual
			<b>F/U Visits:</b> 10% of cases <i>or</i> a minimum of 3 cases	
Level 1	No routine DISC monitoring is required for low-risk studies			
*As applicable				

## **6.0 DATA INTEGRITY AND SAFETY COMMITTEE OPERATIONS**

The UFHCC DISC serves as the default DSMB for UFHCC IITs and other qualifying clinical trials that do not have adequate external oversight, as determined by the SRMC. The DISC is responsible for monitoring the safety and quality assurance of clinical trials in accordance with the DISC Charter.

### **6.1 DISC Mission and Purpose**

The mission of the DISC is to provide oversight and monitoring of trials conducted by the UFHCC, as assigned by the SRMC. The DISC is committed to safeguarding trial subjects and ensuring that the validity and integrity of trial data and operations are upheld.

The DISC is charged with ensuring, through review and recommendations to PIs, the SRMC, and the IRB, trials conducted at the UFHCC are done in a manner that is safe, accurate, and consistent with the protocol in order to meet scientific objectives. The DISC has authority to access research and pertinent clinical records of all patients enrolled in studies that fall under its review. This includes the authority to request and review all data collected and/or generated during the course of a given trial. This is done in the interest of current and future subjects as well as non-study patients that may be impacted by the results of our trials.

DISC is responsible for:

- Review of all trials assigned to the DISC by the SRMC to provide oversight and to confirm safety and related parameters to be monitored, the frequency of committee monitoring reviews and interim safety analyses (as applicable), and the statistical methodologies as specified in the approved protocol are appropriate;
- Examination of endpoint and toxicity data from clinical trials via the predetermined schedule established by the SRMC;
- Recommendations to the PI, and any relevant oversight committees, concerning continuation or modification of clinical trials based upon the observed efficacy or adverse effects due to any of the treatments under study;
- Determination of whether recommendation of clinical trial termination is warranted based on predetermined protocol-specific stopping rules, unexpected toxicities, or significant regulatory or protocol violations;
- Communication of monitoring results directly to the PI and SRMC. For clinical trials where UF is the sponsoring institution, DISC will also communicate directly with the IRB if trial enrollment suspension or trial termination is recommended; and
- Review of protocol violations and other significant findings related to data integrity or quality that may arise and the review of corrective action plans.

### **6.2 Trials Qualifying for DISC Oversight**

SRMC determines the interventional studies in need of DISC monitoring. At a minimum, the DISC oversees interventional UFHCC IITs. The UFHCC DISC serves as the default DSMB for UFHCC IITs and other clinical trials that do not have adequate external oversight, as determined by the SRMC. For non-UFHCC IITs deemed to require DISC oversight, the sponsoring institution must allow DISC to have access to study level data, including safety and efficacy data, as applicable.

The UFHCC requires that all IITs adhere to the UFHCC DSMP. The SRMC will confirm that each interventional trial has a trial-specific DSMP included within the protocol or as an accompanying document that specifies interim analyses and stopping rules where pertinent. The UFHCC DSMP mandates that all IITs (particularly those involving investigational procedures) considered to be very high, high, or moderate risk by the SRMC must be overseen by the DISC or another qualified DSMB. Investigational procedures include the use of any technology, radiation, treatment, or other medical intervention. In alignment with the UFHCC DSMP, the SRMC will determine if a proposed external DSMB for an IIT is acceptable.

### **6.3 DISC Membership**

DISC membership includes a Chair, a Vice Chair, and multidisciplinary representation from clinical researchers and biostatisticians. The director of the UFHCC appoints the Chair of the DISC. The director, in consultation

with the DISC Chair, appoints the Vice Chair and voting committee members. At a minimum, the composition of the committee, and any convened board, must include:

### **Voting Members**

- One Chair or Vice-Chair
- Three oncology clinicians (MD/DO/PharmD/ARNP/PA/RN)
- One biostatistician
- Additional voting members as necessary to constitute quorum

### **Non-Voting Member**

- DISC administrator

A research administrator from the UFHCC CRO is assigned to provide administrative support to the DISC. The DISC administrator receives, tracks, and reviews all DISC submissions for completeness. The DISC administrator also ensures trials are reviewed by the DISC and CRO quality assurance staff on the appropriate schedule according to their assigned risk level. The administrator assists the DISC Chair with assigning reviewers for trials and manages meeting agendas, recording of meeting minutes, and generation of formal review documentation. In addition, the DISC administrator tracks committee member attendance and generates reports for the DISC Chair, Cancer Center, and CRO Leadership. DISC membership is separate and distinct from that of SRMC. A list of DISC members can be found in **Appendix D**.

### **6.4 DISC Member Responsibilities**

In order to effectively review trials under the DISC oversight committee, members must:

1. Familiarize themselves with the research protocol(s) under oversight and the study plans for data and safety monitoring.
2. Evaluate data (e.g., protocol-specific data and safety monitoring report, audit report, AEs report, and/or deviations report) to determine protocol progress and whether the trial should continue as originally designed, should be changed, or should be terminated based on these considerations.

Voting members are expected to attend a minimum of 75% of scheduled meetings. Attendance and active participation will be monitored. Management of member COI is discussed in detail elsewhere (see Section 3.0). Members who do not meet the attendance or participation requirements may be removed from the committee at the discretion of the UFHCC Director.

### **6.5 DISC Meetings**

The DISC meets monthly for routine study reviews and on an ad hoc basis as necessary. Meetings may only commence once quorum is met. Quorum for the DISC is defined as participation of at least 5 of the voting members in attendance, including a minimum of the Chair or vice-Chair and one biostatistician. The vice-Chair executes the responsibilities of the Chair when the Chair is unavailable, has a conflict, or is delegated by the Chair. Members vote on DISC actions and recommendations. To vote, a member must be present at the convened scheduled meeting or be a participant through conference calls. A simple majority of members present passes a proposal, motion, or recommendation. When a tie vote occurs, the Chair (or vice-Chair in the Chair's absence/conflict), can cast the deciding vote.

Consistent with the monitoring frequency approved by the SRMC, the assembled DISC reviews AEs, UPs, protocol deviations in summary form, internal and external audit reports, and protocol-specific data and study monitoring reports. The Chair or Vice Chair may review individually reported serious AEs (SAEs), UPs, deviations, or other administrative matters through an expedited process. These may be referred to the full committee at the Chair or Vice Chair's discretion.

Both open and closed sessions may be held. During open sessions, the PI or designee is invited to provide information related to trial progress, safety signals, and any interim statistical analysis that has been completed and answer any questions raised by the committee. The closed sessions, attended only by non-conflicted voting and administrative non-voting committee members, are where the DISC discusses, votes, and makes final recommendations. If there is a tie, the Chair will cast the deciding vote. If the vote did not attain unanimous

support, the recommendations will include a minority report. These recommendations are then sent to the PI and the Chair of the SRMC. All recommendations for enrollment suspension or study termination will be communicated directly to the PI, with copies to the SRMC, ADCI, UFHCC Director, and the UF IRB (only for UFHCC IITs). The PI is responsible for sharing the DSMB reports to the IRB in accordance with IRB requirements.

## **6.6 Protocol Review**

Trials recommended for DISC oversight by the SRMC will be rapidly reviewed by DISC following SRMC approval. This initial review serves to secure DISC involvement, confirm the assigned risk level, and acquaint the committee members with the protocol. This initial review can be done expeditiously via e-mail or other electronic means. Any DISC recommendations to change the assigned risk level, modify the protocol, or administratively modify the monitoring plan must go back through the SRMC for review and ultimate approval. SRMC remains the final decision maker of the risk level and monitoring expectations. All trials subject to DISC oversight must then be reviewed (complete review) within 3 months (for risk level 4) or 6 months (for risk levels 2-3) of the first subject accrual. Trials will remain under DISC oversight for the duration of the active accrual period and until the last subject has completed the study intervention. Trials may be removed from routine DISC oversight once a study is closed to accrual and no subjects have received any study interventions within the past 6 months.

In addition to trials under routine DISC oversight, any trial conducted at UFHCC may be reviewed by the DISC for data integrity or quality concerns. This includes, but is not limited to, significant findings on internal or external auditing and monitoring reports, hospital incident reports, or other concerns related to research conduct. In addition to routine monitoring, individually reported SAEs may be reviewed by the Chair or Vice Chair in an expedited process.

### **6.6.1 Review and Safety Data**

The study team will provide reports of AEs observed in trial participants to the DISC on a regular, pre-determined schedule. Deaths on study or other SAEs will be reported to the DISC Chair and the DISC administrator within 5 business days of discovery. This applies to all SAEs that occur from the time any study intervention is initiated until 30 days following the last protocol intervention, at a minimum. Extended SAE reporting intervals may be required as defined per protocol. All SAEs must be reported regardless of expectedness or relatedness to the intervention. These reports may be reviewed independently and acknowledged by the Chair or Vice Chair. Reports for events that are considered serious, unexpected, and related or that may impact the overall conduct of the study are escalated to the full board to review. To assure patient safety in each trial, the committee will develop individualized methods for monitoring AEs as needed.

### **6.6.2 Review of Protocol Compliance**

Instances of major study deviations, including regulatory and protocol non-compliance, will be reported to the DISC Chair and administrator within 5 business days of discovery. Non-compliance with DISC policies and procedures (e.g., failure to provide study data, access to source, or corrective action plans when requested) will also be considered a major deviation.

### **6.6.3 Review of Efficacy Data**

The investigative team will tabulate efficacy data and provide to the DISC for review on a pre-determined schedule defined in the study protocol's DSMP or as requested by DISC. The DISC will evaluate, as appropriate, outcome data according to guidelines for data monitoring outlined in the study protocol and published policies and procedures. Based on the data reviewed at these interim evaluations, the committee may request additional data or recommend early termination of the trial if stopping rules or futility criteria are met. Stopping rules, if applicable, should be clearly described in the IRB- and SRMC-approved protocol DSMP.

### **6.6.4 Review of Dose Escalation Data**

DISC is responsible for reviewing all potential dose-limiting toxicities for dose escalation studies. Prior to any study being allowed to escalate to the next dose level, the DISC must perform a thorough review of all cumulative toxicities experienced during the review period and determine if the protocol-specified conditions for escalation are met. Continuation to the next dosing cohort is contingent upon the final DISC recommendation.

### **6.6.5 Review of Data Quality and Trial Operations**

To ensure the highest possible quality of data, the committee will regularly monitor study progress in the following aspects:

- Data submission timeliness, particularly in regards to safety and efficacy data;
- Rates of protocol compliance by the PI, study staff, and subjects;
- Study accrual, early subject terminations and withdrawals;
- Study deviations, including regulatory and protocol non-compliance, unblinding, or other UPs;
- Results of any internal or external audits performed on the study;
- Eligibility violations; and
- Any other measures reflective of data integrity or quality.

### **6.7 DISC Recommendations and Communications**

Under the authority of the UFHCC Director, DISC will assess cumulative AEs, UPs, and efficacy data (when appropriate), and determine if the risk-to-benefit ratio of the study remains favorable. In addition, the committee will review serious or continuing protocol non-compliance or data integrity issues discovered by UFHCC CRO quality assurance staff. The DISC has the authority to require the creation and implementation of a CAPA plan or recommend protocol modifications to the PI to address toxicity or other clinical issues. When CAPAs are required, the PI will be responsible for drafting a plan and submitting it in writing to the DISC. DISC will then review the PI's response to ensure any identified deficiencies have been adequately addressed, including plans to mitigate future occurrences. Once a CAPA plan has been approved and implemented, the DISC will determine if a re-audit or re-review is required. If the CAPA plan is insufficient or if the deficiencies warrant, the DISC may recommend suspension of further study activity or research activities for individual investigators or study team members. Any DISC recommendation to suspend or terminate a study will be communicated directly to the PI, with copies to the SRMC, ADCI, UFHCC Director, and UF IRB. While DISC has the independent authority to recommend the suspension or termination of a clinical trial, all actions of this nature will involve the PI and ultimately require IRB and/or SRMC review and approval. In this way, administrative authority for timely implementation of DISC recommendations always resides with the PI.

#### **6.7.1 DISC Final Recommendations**

DISC may make the following recommendations after review of trial activity:

- *Study continuation as planned*: There are no outstanding subject safety or data integrity issues; accrual may continue; no further action is required. Non-binding recommendations may be provided.
- *Study continuation with stipulations and/or modifications*: There are questions regarding subject safety or data integrity; questions require a written response or modification to the study protocol; accrual may continue pending committee receipt of an acceptable PI response. Requested stipulations or modifications meeting the definition of a major amendment per the SRMC Policies and Procedures Manual will require SRMC and IRB approvals after adoption by the PI.
- *Study suspension with stipulations and/or modifications*: There are concerns regarding subject safety or data integrity that require an expedited response from the PI; accrual must be suspended until concerns are resolved.
- *Study termination*: There are issues that warrant immediate suspension of further accrual with or without discontinuation of study interventions for current subjects.

#### **6.7.2 Decision Reporting**

The DISC administrator will be responsible for recording and compiling meeting minutes and communicating recommendations to the PI in writing. A report is generated each time a study is reviewed by the committee or undergoes an expedited review. The PI should acknowledge or respond to each memorandum released by the DISC. The PI is responsible for reporting DISC memoranda to the IRB of record per the IRB's policies and procedures. There is no appeal process for final DISC recommendations.

In general, confidential outcome information will not be released while a trial is actively enrolling or interventions are ongoing. Any analysis of outcome data performed by the DISC may not be released to the PI without approval from the DISC Chair.

Review dates, agendas, recommendations, and communication records will be kept in the OnCore database by the DISC administrator.

## **6.8 Confidentiality**

All appointed DISC members are expected to maintain confidentiality. Informal communications, written or verbal, including committee deliberations, findings and recommendations may not be disseminated outside of DISC. Outcome data for protocols still enrolling subjects are considered confidential and are not to be discussed outside the DISC meetings with anyone other than study team members. Any special release of these data should be approved by the DISC Chair or Vice Chair.

## **7.0 QUALITY ASSURANCE AND QUALITY CONTROL**

The Quality Assurance and Quality Control initiatives are a major component of the DSMP and ensures high standards for clinical trial data collection and management. The UFHCC Compliance Group oversees the quality assurance and quality control responsibilities of the DSMP and the overall Research Oversight System. This group works in conjunction with the CRO Leadership to facilitate the connection between compliance operations and continued education throughout the oncology research enterprise.

A detailed description of the UFHCC Compliance Group (membership and operations) can be found in the UFHCC Audit Manual [4].

The UFHCC CRO Compliance Group performs a variety of functions:

- Coordinating the clinical trials audit process
- Collaborates with PIs to develop source documentation forms and conduct site initiation visits (SIVs) for all IITs,
- Collaborates with PIs to develop study specific monitoring plans,
- Collaborates with the CRO Education & Training Coordinator to create needed training programs,
- Auditing and monitoring UFHCC IIT protocols,
- Auditing for the DISC,
- Auditing external studies as required under this DSMP,
- Reporting audit findings to the CRO Leadership,
- Assisting investigators with external audits and monitoring visits,
- Assisting investigators with the development and implementation of CAPA plans,
- Participating in clinical research training and education,
- Developing SOPs, policies, and guidelines, and
- Implementing policies and guidelines as needed for the clinical trial process

UFHCC CRO quality assurance staff conduct audits of all clinical trials conducted by the UFHCC and UF IITs and NCTN/ETCTN studies conducted by affiliate sites. The guidelines followed are consistent with those established by the Clinical Trials Monitoring Branch of the NCI. Audits include an independent review protocol and regulatory compliance for patient consent, eligibility, treatment administration, response evaluation, AEs, UPs, overall data quality, IRB documentation, and pharmacy record keeping. These audits insure centralized oversight and uniform trial compliance is being followed across the center.

### **7.1 Quality Assurance Activities**

Quality assurance activities are defined by ICH E6 1.46 as “all those planned and systematic actions that are established to ensure that the trial is performed and data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirements.”

Auditing is a function that is distinct from routine monitoring and quality control processes. The primary purpose of an audit is to evaluate overall study conduct and compliance with the protocol, SOPs, GCP, and regulatory requirements at a very high level. This is not interchangeable with monitoring, which is a continuous function, although there is overlap with the study content that is reviewed.

## **7.2 Quality Control Activities**

Quality control activities are defined by ICH E6 1.46 as “the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for the quality of the trial-related activities are fulfilled.”

Per ICH E6 guidelines, sponsors must ensure that their trials are conducted under an adequate monitoring plan. The amount of monitoring that is required is based upon the type of study and its risk level. All UF-sponsored IITs must have a study-specific monitoring plan. The determination of the extent and nature of monitoring should be based on considerations such as the objective, risk level, design, complexity, blinding, size, and endpoints of the trial. In general, there is a need for some on-site monitoring. However, central monitoring in conjunction with training and written guidance can assure appropriate conduct of the trial in accordance with GCP. Risk-based monitoring is an appropriate approach for UF-sponsored IITs. Study teams are responsible for conducting quality control activities for studies that require additional monitoring beyond the minimums laid out in this DSMP.

## **7.3 Protocol Selection**

All new interventional trials approved by SRMC are catalogued by the UFHCC CRO and assigned audit frequencies based on **Table 3**. The lead auditor is responsible for selecting and scheduling audits. Audits of UFHCC clinical trials will be scheduled according to the guidelines outlined in this UFHCC DSMP.

<b>Table 3. Guidelines for UFHCC CRO Audit Frequency</b>	
<b>Protocol Prioritization</b>	<b>Audit Frequency</b>
UF IIT or DISC monitoring required	Follows the monitoring frequency chart found in <b>Section 5.1.1</b> .
UF IITs conducted at Academic Research Consortium Sites	At a minimum, the first subject enrolled on a UF IIT protocol at a UFHCC Academic Research Consortium member site will be audited. This is in addition to the level of monitoring required per assigned monitoring plan for that specific protocol.
NCTN/ETCTN trials	At a minimum, each NCTN/ETCTN study will be audited annually. At least 10% or a minimum of 2 cases will be selected from each study.
Externally sponsored studies	At a minimum, two externally sponsored studies from each DSG (not including NCTN or ETCTN trials) will be audited annually. At least one case will be selected from each study.
Protocols led by first-time UF PI	At a minimum, the first subject enrolled and up to 3 additional subjects will be audited within the study’s first year. One protocol will be selected as part of a first-time UF PI audit. Additional protocols may be selected based on the audit findings.
Protocols facilitated by new coordinator	At a minimum, the first subject enrolled and up to 3 additional subjects will be audited within the study’s first year. One protocol will be selected as part of a new coordinator audit. Additional protocols may be selected based on the audit findings.
For cause	As needed.

## **7.4 Subject Selection**

Subject selection for routine audits will be completed using an internally-created, computerized randomizing program and will represent a minimum number of consented study subjects for the selected protocol. The number of subjects selected may vary depending on the type and risk assessment level of the protocol selected for an audit and the number of enrolled participants. Subject selection is random, impartial, and will consider subjects accrued during the specified audit review period. In order to maintain the highest quality protocol-specific research data, subject charts will be audited thoroughly for informed consent documentation, original source documentation required to support protocol compliance, and other relevant information. Usually, only cases entered since the last audit will be selected, but any accrued cases (even those that were previously audited) might be selected. In situations where a previously audited case is selected, only activities occurring after the prior audit will be reviewed.

## **7.5 Audit Findings**

Once the internal audit is complete, the UFHCC CRO quality assurance staff will conduct an exit interview with the PI and study team to discuss preliminary findings and then generates a complete report of findings. All reports will be viewed and approved by the Assistant Director of Clinical Research Administration and Compliance. Final reports will be distributed to the PI and DISC administrator (if applicable) following the exit interview. **Table 4** contains the criteria used for a UFHCC final audit report.

<b>Table 4. UFHCC Audit Result Categories</b>	
<b>Audit Evaluation</b>	<b>Criteria</b>
Exceptional	Complete source documentation, outstanding data quality, protocol compliance, and regulatory compliance demonstrated. No major violations. <ul style="list-style-type: none"> <li>• No major violations</li> <li>• ≤1 lesser violation per audited case</li> <li>• PI acknowledgement required</li> </ul>
Satisfactory	No major violations <ul style="list-style-type: none"> <li>• ≤3 lesser violations per audited case</li> <li>• PI acknowledgement required</li> </ul>
Satisfactory, needs follow up	One or more major violations (ratio of major to audited cases <0.5) <ul style="list-style-type: none"> <li>• Four to 6 lesser violations per audited case</li> <li>• PI response and CAPA plan required</li> </ul>
Unacceptable	Critical or major violations (ratio of major to audited cases ≥0.5) <ul style="list-style-type: none"> <li>• A single life-threatening major violation on a subject case</li> <li>• A single major violation that questions the PI's available to conduct research per established regulations and policies</li> <li>• Excessive lesser violations (&gt;6 per audited case)</li> <li>• Misconduct or fraud</li> <li>• PI response and CAPA plan required.</li> </ul>

### **7.5.1 Deficiencies**

Critical, major, and lesser deficiencies are determined per NCI guidelines established by the Clinical Trials Monitoring Branch of the NCI when grading audit findings. General guidelines for interpretation of major and lesser deficiencies include:

- Major deficiencies are considered serious and require corrective action by the PI and the study team.
- Lesser deficiencies are expected to occur occasionally. The Compliance Group evaluates the number of such lesser deficiencies and observes for patterns.

If during an audit, a subject safety risk is discovered, the UFHCC CRO quality assurance staff must notify the ADCI and the Compliance Group immediately. The members must review the violations (in person or remotely) and determine if the audit results should be submitted to the DISC for expedited review. The DISC has an opportunity at this point to recommend immediate action to the PI, such as closure of accrual and/or conduct or suspension of the protocol, if it is deemed necessary. Any DISC recommendation to suspend or terminate a study will be communicated directly to the PI, with copies to the SRMC, ADCI, UFHCC Director, and the UF IRB. Immediate action by the DISC would take place in the event of suspected subject safety risks, research fraud, or an extremely deficient audit.

### **7.6 Audit Response Review and Submission**

A report detailing the initial audit findings, who was present during the exit interview, clarifications by the staff, and any recommendations by the UFHCC CRO quality assurance staff will be submitted to the PI and the primary study coordinator within 5 business days following the exit interview. The PI will have 5 business days to acknowledge the report and address the findings, if required, for audits that are evaluated as "Satisfactory, needs follow up." For the reports that include critical or major deficiencies, the PI must respond with a CAPA plan within 5 business days. After the receipt of the PI's response and CAPA plan, if applicable, a final copy of the detailed report of audit findings and PI's response will be presented to DISC for review. If the PI fails to provide a response

within the allotted time frame or the response is inadequate then the DISC may recommend study suspension to the SRMC until an acceptable response is received, or terminated, per the discretion of the DISC Chair or Vice Chair.

## **7.7 Corrective and Preventative Action Plans**

Audits resulting in a “Satisfactory, needs follow-up” **may** require a CAPA plan to address the observed deficiencies. If a CAPA plan is required, this will be communicated in the audit letter provided to the study team. All audits that result in “Unacceptable” **will** require a CAPA plan to address any observed deficiencies. The timing of CAPA plan submission is outlined above.

## **7.8 Education and Training of Research Staff**

Training and continuing education is a large component of the UFHCC CRO. The CRO has set standards for the execution and management of all types of cancer clinical trials conducted by the UFHCC. These standards apply to the entire life cycle of each clinical trial that is overseen by the UFHCC. UFHCC CRO staff lead the development and delivery of educational materials and training program requirements.

Each staff member of the UFHCC CRO undergoes a thorough orientation period and ongoing education program that is managed by the applicable group manager and the Education and Training Coordinator. These education requirements apply to all clinical and regulatory divisions of the CRO. To fulfill GCP requirements, all staff will have appropriate education and training specific to their role in the clinical trial process. Internal audit findings and reports by the quality assurance staff will be used to determine if additional training, SOPs, or policy revisions are necessary. Metrics related to UFHCC CRO staff education, training, and quality assurance performance are maintained by the Education and Training Coordinator. These staff metrics are reviewed, at a minimum, as part of annual performance evaluations.

CRO leadership will also monitor for any additional educational training opportunities to benefit study team members including PIs. The Education and Training Coordinator will be consulted as necessary to tailor educational resources or develop new programs to support groups of investigators if trends are noted.

## **8.0 SAFETY REPORTING**

### **8.1 General Guidelines**

All protocols must outline the parameters for routine and expedited AE and UP reporting. For studies involving investigational drugs, devices, or clinical procedures, the protocol must define the event grading criteria to be used (e.g., the Common Terminology Criteria for Adverse Events) and the mechanism for confirming event attributions. Protocols should also include a description of the processes for internal and external event reporting. AE and UP reporting requirements may vary depending on the purpose, phase, and complexity of the study. Investigators are responsible for promptly identifying and reporting AEs, which includes grade, attribution, and expectedness, to the sponsor, DISC, and IRB as required per protocol and per local policies and procedures. Additional guidelines for reporting of AEs can be found within the NCI Investigator Handbook [5]. UFHCC holds all investigators involved in cancer-relevant research accountable to the minimum expectations and standards from this benchmarked reference.

### **8.2 Routine Reporting**

All routine AEs, their grade, attribution, and expectedness should be captured per protocol within study case report forms. For IITs, these should be captured in such a way that events can be exported in aggregate for review by the PI, the DISC, and other parties as required.

### **8.3 Expedited Reporting**

Expedited safety reporting is required for any event that meets the FDA’s definition of “serious.” The FDA considered any event that meets one or more of the following criteria to be an SAE:

- Death;
- Life-threatening event;
- Hospitalization (initial or prolonged);
- Disability or permanent damage;

- Congenital anomaly/birth defect;
- Other serious (important medical events).

There may also be protocol-specific AEs of significant interest. The reporting of these should be defined in a protocol-specific manner, but in general, they should be treated as an SAE. For example, for immuno-oncology studies, some AEs of particular importance, described in the protocol, are treated and/or reported like SAEs. In addition to SAE reporting, events meeting the Office of Human Research Protections definition of an UP must also undergo expedited reporting.

According to the Office of Human Research Protections, the phrase “unanticipated problems involving risks to subjects or others” is found but not defined in the HHS regulations at 45 C.F.R. § 46. The Office of Human Research Protections considers UPs, 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 research places subjects, or others, at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Events that are considered serious or unanticipated must be reported to the sponsor within the protocol-specified period. The PI or their designee must review all events before they are reported to any external entity or to the DISC. The PI or their designee is responsible for assigning a preliminary AE term, grade, and attribution prior to submission of the initial AE report. The PI or their designee should also review and sign off on any interim and final event reports that are disseminated to any oversight body.

### **8.3.1 Expedited Reporting for IITs**

Any SAE or UP that occurs on a UF IIT must be reported to the UFHCC DISC, in addition to any applicable external collaborators (**Appendix E**). The DISC should be apprised of SAE/UPs within five business days of discovery. This applies to all SAEs/UPs that occur from the time any study intervention is initiated until 30 days following the last protocol intervention at a minimum. Extended SAE/UP reporting intervals may be required as defined per protocol. External sponsors and/or collaborators should be notified within the time frame specified by the protocol. The PI is also responsible for notifying the FDA, Office of Science Policy, if applicable, for SAEs that occur on protocols that fall under their oversight.

- DISC – Within 5 business days
- Sponsor/External Collaborator – Per the protocol-specified timelines
- FDA – Use FDA Form 3500 to report per the regulations set forth in 21 C.F.R. § 312.32
- Office of Science Policy – Within 15 days or 7 days for fatal/life-threatening events.
- IRB – Refer to the SAE/UP reporting guidelines for the applicable IRB
- Other regulatory bodies as applicable

For events on UF IITs that originate outside of the institution, the local PI or their designee must notify the designated UF contact within **one** business day of discovery. The local PI is also responsible for reporting the event to any sponsors/external collaborators as required by the protocol document. The overall PI assumes all responsibility for making a final assessment of the event and communicating the event and outcome to the DISC, IRB, FDA, and/or Office of Science Policy.

## **9.0 MULTI-INSTITUTIONAL TRIAL ADMINISTRATION**

The UFHCC CRO supports a regional network for UF IITs and other high priority clinical trials. The UFHCC Academic Research Consortium is administratively managed within the CRO. Such trials are governed by the policies in this DSMP and the UFHCC Research Oversight System.

## **9.1 Site Evaluation Process**

Every potential consortium site must submit a qualification packet to the Academic Research Consortium coordinator for initial consideration of inclusion in the Academic Research Consortium Network. A study-specific questionnaire will be completed by the site. The qualification packet allows sites to explain their organizational and clinical capabilities and resources. Participating sites will be selected based upon review of their questionnaire responses, anticipated accrual, and prior data quality index performance on UF IITs.

Sites applying for Academic Research Consortium membership will be reviewed by the ADCI and UFHCC Director. Approval for Academic Research Consortium membership will be initially termed on a one-year probationary period regardless of tier level assigned. Tier levels assignments relate to the local site infrastructure, capacity, and needs and experience related to prior clinical investigation. Performance progress reports and continuing expectations are provided to the Network sites annually. UFHCC Academic Research Consortium tier levels are associated with the following trial relationships including escalating expectations:

- **Tier 1:** NCTN
- **Tier 2:** Tier 1 plus access to select UF IITs
- **Tier 3:** Tier 2 plus consortium studies, select ETCTN trials and the opportunity for Commission on Cancer Accreditation through the Integrated Network Cancer Program

## **9.2 Site Initiation Visits**

UF will conduct an SIV for each participating site. This visit will cover information related to protocol objectives, design, study assessments, data submission, and data and safety monitoring. Each site is expected to fully comply with the requirements of this document. In addition, sites must adhere to the data management plan devised for each protocol including any data monitoring requirements that extend beyond the requirements of this plan. Attendees for each SIV will be recorded and a follow-up letter summarizing the content of the SIV and the site's activation date will be provided to the local site PI.

## **9.3 External Site Communication**

If the UFHCC is acting as the coordinating center for multi-institutional studies, it is the responsibility of the lead PI or their designee to ensure all data, safety events, and UPs are submitted per protocol and regulatory requirements. All sites should conform to the data safety and monitoring policies as outlined above.

Working with the UFHCC CRO, the PI should develop a comprehensive study-specific manual of procedures for non-UFHCC sites that minimally includes:

1. Contact information for key study personnel;
2. Communication plan;
3. Central regulatory tracking plan;
4. Central eligibility review process;
5. Overview of the management plan;
6. Description of the exception/deviation reporting/response process;
7. Description of AEs, adverse drug reaction, SAE, and serious adverse drug reactions reporting process;
8. Description of agent/device accountability;
9. Description of the monitoring expectations and monitoring plan and timeline;
10. Description of early termination and/or close out process.

PIs sponsoring multi-center UFHCC IITs must identify a primary liaison to coordinate trial logistics and provide oversight management of each network site. The liaison or their designee will be responsible for providing affiliates with protocol amendments, study-specific manuals or SOPs, and routine and urgent study communications.

## **10.0 ONCORE**

OnCore serves as the CTMS of record for all cancer-relevant clinical trials that are subject to oversight under this DSMP. The CTMS must be fully utilized to capture relevant IRB and ancillary committee review information. In addition, all subjects consented or enrolled to these research studies must be registered within the system and attached to the appropriate protocol entry per UFHCC SOP ADM-004 [6]. Utilization of the CTMS for both

study and subject status information is essential to the success of this plan and is thus required. Members of the Research Oversight System will have administrative access to the information contained within the CTMS in order to carry out their duties as described within this document.

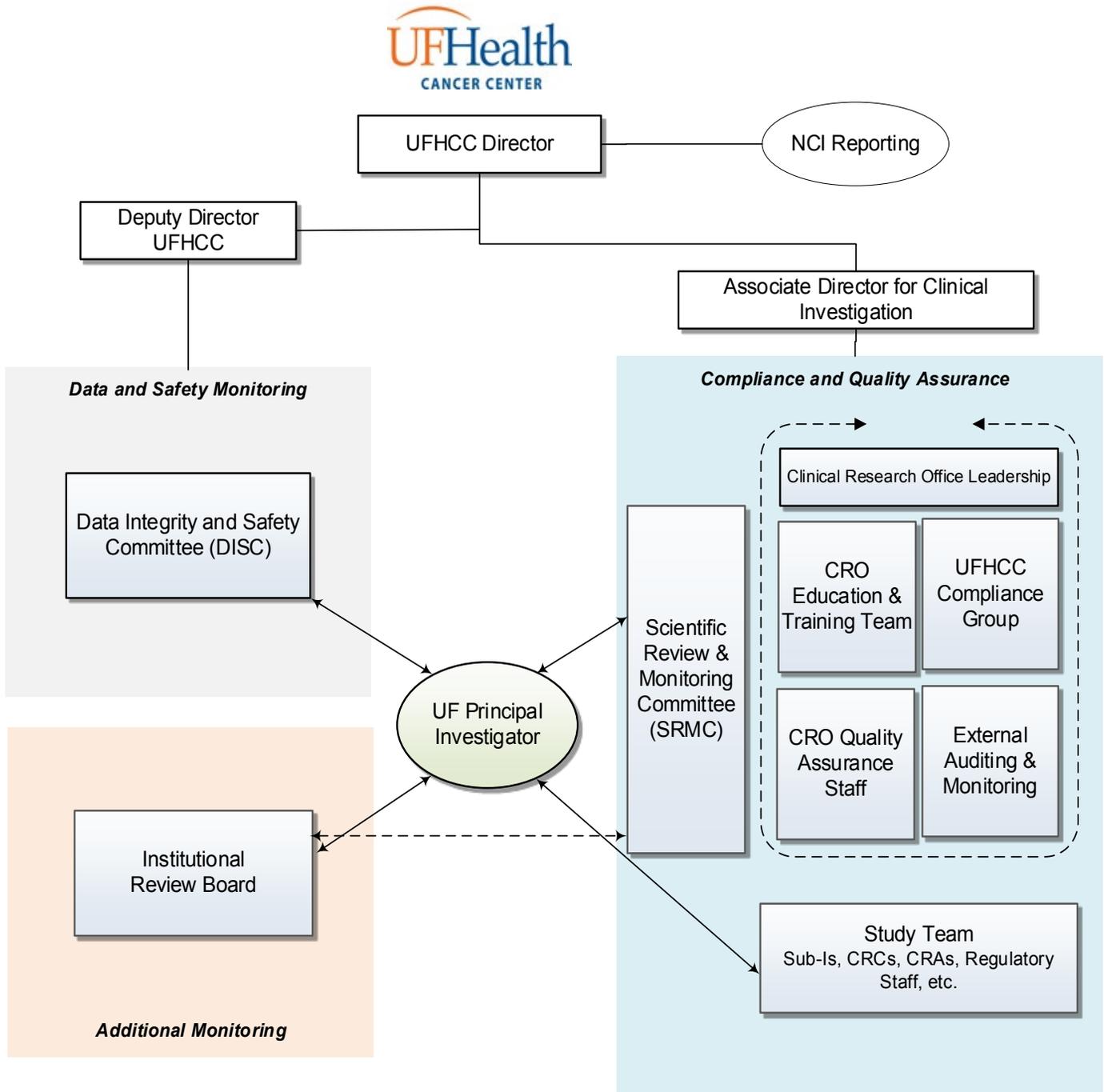
## 11.0 REFERENCE LIST

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- [5] National Cancer Institute, Division of Cancer Treatment & Diagnosis. A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI. URL: <https://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf>. Accessed: 10/02/2018.
- [6] UF Health Cancer Center, Clinical Research Office. Standard Operating Procedure: Data Requirement for Cancer Center Reporting. Procedure Number: ADM-004. October 12, 2018.

## 12.0 APPENDICES

- A. Research Oversight System Flow Chart
- B. Disease Site Groups List
- C. Prioritization Scores
- D. DISC Membership List
- E. Expedited Reporting

### Appendix A: Research Oversight System Flow Chart



## Appendix B: Disease Site Groups List

<b>Appendix B. UFHCC Disease Site Groups (DSGs)</b>	
<b>Disease-Specific Groups</b>	<b>Name/Department</b>
<b>Breast</b>	<b>Karen Daily, DO / HemOnc</b> Lisa Spiguel, MD / Surgery Natalie Lockney, MD / RadOnc
<b>Gastrointestinal</b>	<b>Thomas J. George, MD / HemOnc</b> Steven Hughes, MD / SurgOnc
<b>Genitourinary</b>	<b>Paul Crispen, MD / Urology</b> Robert Zlotecki, MD, PhD / RadOnc
<b>Gynecologic</b>	<b>Merry-Jennifer Markham, MD / HemOnc</b> Jacqueline Castagno, MD / ObGyn
<b>Head &amp; Neck</b>	<b>Natalie Silver, MD / ENT</b> Robert Amdur, MD / RadOnc Peter Dziegielewski, MD / ENT
<b>Hematologic Malignancies</b>	<b>Maxim Norkin, MD, PhD / HemOnc</b> Randall Brown, MD / HemOnc Jack Hsu, MD / HemOnc
<b>Neuro-Oncology</b>	<b>David Tran, MD, PhD / MedOnc</b> Maryam Rahman, MD / Neurosurgery
<b>Pediatrics</b>	<b>Sridharan Gururangan, FRCP / Peds</b> William Slayton, MD / Peds
<b>Sarcoma &amp; Cutaneous</b>	<b>Christiana Shaw, MD / Surgery</b> Andre Spieguel, MD / Orthopedics Joanne Lagmay, MD / Peds
<b>Thoracic</b>	<b>Frederic Kaye, MD, PhD / HemOnc</b> Hiren Mehta, MD / Pulmonary Tiago Machuca, MD / Thoracic Surgery
<b>Disease-Agnostic Groups</b>	<b>Name/Department/Division</b>
<b>Cancer Population Sciences</b>	<b>Janice Krieger, PhD / Communication &amp; Journalism</b> <b>Diana Wilkie, PhD, RN / Nursing Science &amp; Palliative Care</b>
<b>Experimental Therapeutics</b>	<b>David DeRemer, PharmD / Pharmacotherapy</b> <b>Thomas J. George, MD / HemOnc</b>
<b>Bold = Research Leader(s)</b>	

**Appendix C: Prioritization Scores**

<b>Appendix C. Prioritization Scores</b>		
<b>ORIGINATOR</b>	<b>STUDY TYPE</b>	<b>PRIORITIZATION SCORE</b>
<b>UFHCC Faculty Developed Studies</b>	Treatment, Pilot/feasibility, Phase I	1
	Treatment, Phase I/II, II, III	2
	Interventional Non-Treatment, Any Phase	3
	Non-Interventional, Prospective	10
	Non-Interventional, Retrospective	13
<b>NCI-NCTN Cooperative Group</b>	Treatment, Any Phase	4
	Interventional Non-Treatment, Any Phase	7
	Non-Interventional	11
<b>Foundation/External Academic</b>	Treatment, Any Phase	5
	Interventional Non-Treatment, Any Phase	8
	Non-Interventional	14
<b>Industry</b>	Treatment, Phase I, I/II, II	6
	Treatment, Phase III	9
	Interventional Non-Treatment, Any Phase	12
	Non-Interventional	15

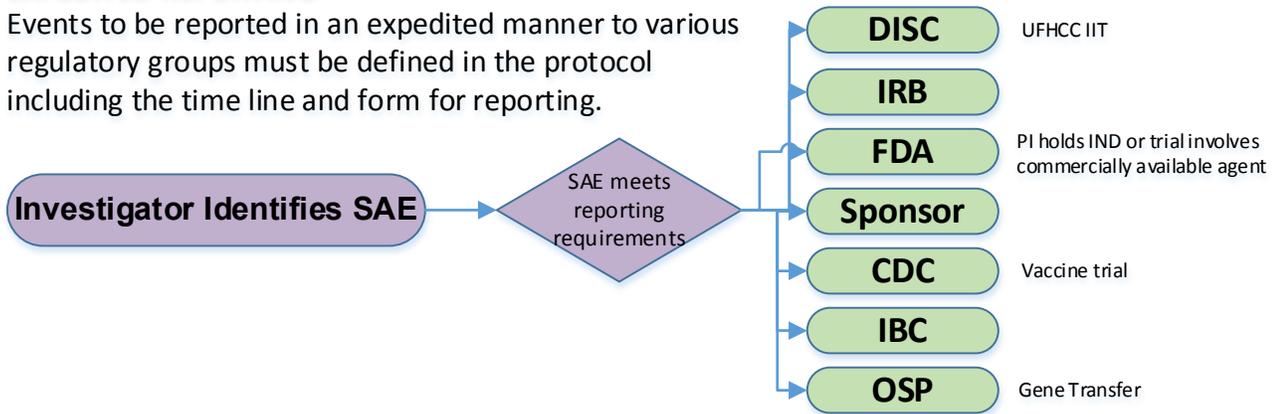
**Appendix D: DISC Membership List**

<b>Appendix D. DISC Membership List</b>		
<b>First and Last Name, Degree</b>	<b>Position</b>	<b>Specialty</b>
John Wingard, MD	Chair	Medical Oncology
Merry-Jennifer Markham, MD	Vice-Chair	Medical Oncology
Julie A. Bradley, MD	Voting Member	Radiation Oncology
Paul Castillo, MD	Voting Member	Medical Oncology
Nam Dang, MD, PhD	Voting Member	Medical Oncology
Sridharan Gururangan, FRCP	Voting Member	Neuro-oncology
Kathryn Hitchcock, MD, PhD	Voting Member	Radiation Oncology
Bradford S. Hoppe, MD, MPH	Voting Member	Radiation Oncology
Jack Hsu, MD	Voting Member	Medical Oncology
Susan McGorray, PhD	Voting Member	Biostatistics
Martina Murphy, MD	Voting Member	Hematology
Hemant S. Murthy, MD	Voting Member	Medical Oncology
Leslie Pettiford, RN, MS	Voting Member	Research Nursing

## Appendix E: Expedited Reporting

### EXPEDITED REPORTING

Events to be reported in an expedited manner to various regulatory groups must be defined in the protocol including the time line and form for reporting.



**Abbreviations:** CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; IBC, Institutional Biosafety Committee; IRB, institutional review board; OSP, Office of Science Policy; SAE, serious adverse events.