



**University of Florida Health Cancer Center**

**Data Integrity and Safety Committee (DISC) Charter**

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**University of Florida Health Cancer Center**

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**Abbreviations**

AE	Adverse event
CAPA	Corrective and preventative action
DISC	Data Integrity and Safety Committee
DSG	Disease site group
DSMB	Data and safety monitoring board
DSMP	Data and safety monitoring plan
FDA	Food and Drug Administration
IIT	Investigator-initiated trial
IND	Investigational new drug
IRB	Institutional review board
NCI	National Cancer Institute
NIH	National Institutes of Health
PI	Principal investigator
SAE	Serious adverse event
SRMC	Scientific Review and Monitoring Committee
UFHCC	University of Florida Health Cancer Center

## **Introduction**

The University of Florida Health Cancer Center (UFHCC) has a robust research oversight system facilitated through Disease Site Groups (DSGs), the Scientific Review and Monitoring Committee (SRMC), and the Data Integrity and Safety Committee (DISC). All cancer relevant clinical trials are initially vetted through peer review at one of UFHCC's DSGs and then submitted for review and approval by the SRMC. As authorized by the UFHCC Director, the SRMC reviews each trial's proposed data and safety monitoring plan (DSMP) and, if needed, assigns a data and safety monitoring board. The UFHCC DISC serves as the default data and safety monitoring board for UFHCC investigator-initiated trials (IITs) and other qualifying clinical trials that do not have adequate external oversight, as determined by SRMC. The DISC is then responsible for monitoring the safety and quality assurance of clinical trials in accordance with this Charter.

## **Mission**

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.

## **Responsibilities**

The DISC is charged with ensuring, through review and recommendations to principal investigators (PIs), the SRMC, and the institutional review board (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.

## **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

### Non-Voting Member

- DISC administrator

### ***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 (i.e., protocol-specific data and safety monitoring report, audit report, adverse events (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. Members who do not meet the attendance or participation requirements may be removed from the committee at the discretion of the director.

### **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, unanticipated problems, 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 adverse events (SAEs), unanticipated problems, 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 principal investigator or designee is invited to provide information related to trial progress, safety signals, and any interim statistical analysis that has been completed. 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 reviewed by the UFHCC Director (or his/her authorized delegate) prior to releasing the recommendation letter to the PI, the SRMC, and the IRB (only for UFHCC IITs).

## **Trials Qualifying for DISC Oversight**

According to the National Cancer Institute, a clinical trial is “a prospective study involving human subjects designed to answer specific questions about the effects or impact of a particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies.” Trial participants may include cancer patients or persons without cancer. Studies that include nutritional, behavioral, and psychosocial interventions are considered to be clinical trials. Studies evaluating diagnostics (i.e., imaging, etc.) in which findings alter the patient’s clinical care are also considered to be clinical trials. Observational studies, epidemiologic studies, studies of diagnostics that do not affect patient care, and studies that do not test interventions are not considered to be clinical trials.

The DISC oversees interventional trials conducted by sponsor-investigators (hereafter referred to as IITs). The Food and Drug Administration (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.*” The UFHCC DISC serves as the default data and safety monitoring board 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.

Trials subject to this plan may include those supported via externally peer-reviewed grants (National Institutes of Health [NIH], National Cancer Institute [NCI], or other agencies), foundation or sponsor grants or gifts, funding from pharmaceutical companies, or through internal funding mechanisms. UFHCC requires that all IITs adhere to the center’s DSMP. SRMC will confirm that each 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 DSMB for an IIT is acceptable.

## **Risk Assessment**

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, such as 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 drug, 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.

## **Protocol Review**

Trials recommended for DISC oversight by the SRMC will be reviewed by DISC following SRMC approval. This initial review serves to assess the appropriateness of 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 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.

## ***Review of 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 (thirty) 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. 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.

### ***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.

### ***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.

### ***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.

### ***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, including early subject terminations and withdrawals;
- Study deviations, including regulatory and protocol non-compliance, unbinding, or other unanticipated problems;
- Results of any internal or external audits performed on the study;
- Eligibility violations; and
- Any other measures reflective of data integrity or quality.

### **Data Preparation for DISC Review**

The DISC administrator will compile a data integrity and safety monitoring report from OnCore. This report will be forwarded by the DISC administrator to the study team for review at least 3 weeks prior to any pre-scheduled meeting. The study team will return the report with corrections and comments to the DISC administrator at least 2 weeks before the meeting. The report will include the efficacy data relevant to an interim analysis or endpoints requiring review by DISC, all safety data collected to date along with a listing of cumulative deviations, and summary of enrollment data trends.

### **Monitoring Activities**

All trials being conducted under sponsor-investigator INDs must, by federal regulations, be continuously monitored. Other internally sponsored trials may warrant similar continuous observation. Additionally, the DISC will review all written reports of all unacceptable audit findings for any internal or external audit conducted on a UFHCC clinical trial.

The chart below represents the minimum frequency of IIT monitoring for each risk level. Additional monitoring beyond the time points below may be necessary as part of a pre-determined interim analysis or at the discretion of the DISC chair or committee.

<b>Monitoring by Risk Level</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>
<b>Level 4</b>	Quarterly	Quarterly	<b>1<sup>st</sup> Visit:</b> 100% of cases	Semi-Annual
			<b>F/U Visits:</b> 50% of cases or a minimum of 3 cases	
<b>Level 3</b>	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 or a minimum of 3 cases	
<b>Level 2</b>	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 or a minimum of 3 cases	
<b>Level 1</b>	No routine DISC monitoring is required for low risk studies			
<b>*As applicable</b>				

**DISC Recommendations and Communications**

Under the authority of the UFHCC Director, DISC will assess cumulative AEs, unanticipated problems, 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 the Clinical Trials Audit Team. The DISC has the authority to require the creation and implementation of a Corrective and Preventative Action (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, Associate Director of Clinical Investigation, UFHCC Director, and the 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.

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.

## **DISC Reporting**

The DISC administrator will be responsible for recording and compiling meeting minutes and communicating recommendations 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.

## **Conflicts of Interest**

All DISC members must disclose any actual or potential conflicts of interest to the UFHCC Director and the Office of Research per UF policy. Conflicts may include professional interest, proprietary interest, and miscellaneous interest as described in UF's Conflict of Interest and Outside Activities Policy document, <http://generalcounsel.ufl.edu/media/generalcounselufledu/documents/COI.pdf>. Conflicts that arise during a DISC member's tenure must be disclosed and addressed.

Members of the DISC shall not review trials that they are involved in as a PI, co-investigator or consultant in any capacity. These members must recuse themselves from all closed discussions about the trial. In the event that recusal results in quorum no longer being met, the DISC chair may appoint an ad hoc member to monitor that protocol only.

## **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.