UI Health | UIC
UNIVERSITY OF ILLINOIS CANCER CENTER

DATA SAFETY MONITORING COMMITTEE

University of Illinois Cancer Center Data and Safety Monitoring Plan (DSMP)

Policy Release:

The following UICC Data and Safety Monitoring Plan (DSMP) was developed to provide guidance, policies and processes that will ensure oversight and coordination for data and safety monitoring for allcancer-related trials pursuant to the current National Institutes of Health (NIH) Policy for Data and Safety Monitoring and the National Cancer Institute's Cancer Center Support Grant (CCSG) Data and Safety Monitoring guidelines for NCI-designated Cancer Centers.

Version:	11
Last Reviewed:	4/26/2024
Effective Date:	4/29/2024

Cancer Center Approval

Title: Associate Director of Clinical Research

Approval Signature: **Date:**

Electronically signed by: Oana Danciu
Reason: Approver
Date: Apr 29, 2024 15:39 CDT

4/29/2024

Data & Safety Monitoring Plan Revision History

Version #	Date	Section	Details of Changes
11	4/26/2024	Multiple	Clarifications requested by NCI
10	4/23/2024	5.7	Addition that members may not simultaneously serve on other committees or roles
9	1/30/2024	5.6	Added DSMC Member training procedure
8	1/11/2022	5.12 Frequency of Trial Review	Clarification to review routine reports up until the study closes to accrual, and reviewing any SAE's and PD's up until IRB study closure
8	1/11/2022	5.1 Role	Removal of reviewing final results for accuracy and completeness of data
7	8/14/2020	3.4 Protocol Review Committee (PRC)	Revision to match PRC Policy guidelines
7	8/14/2020	5.5 Membership Appointments	Revision to conclude that the Cancer Center Director will review and approve membership of the DSMC
7	8/14/2020	Appendix 3: DSMC Summary Report	Revision to include all reports being used for Routine Summary Reports.
7	8/14/2020	General Policy	Addition of Vice Chair role
6	1/13/2020	2.2.1 Externally Monitored Studies	Clarification and addition of point "d" to allow safety oversight for UICC studies by other NCI Designated Cancer Centers.

6	1/13/2020	2.2.2 UICC-Monitored Studies	Clarification to allow safety oversight for UICC studies by other NCI Designated Cancer Centers.
6	1/13/2020	Appendix 4: Medical Monitor Report Template	Revision of Medical Monitor Form to improve documentation and medical monitor requests for SAE, Protocol Deviation, Dose Escalation, Cohort Expansion, and Routine Reviews.

Table of Contents

1. Introduction

The University of Illinois Cancer Center (UICC) places the highest priority on ensuring the safety of patients who participate in clinical trials. All clinical trials conducted at the UICC must include provisions for data and safety monitoring.

The following UICC Data and Safety Monitoring Plan (DSMP) was developed to provide guidance, policies and processes that will ensure oversight and coordination for data and safety monitoring for all cancer-related trials pursuant to the current National Institutes of Health (NIH) Policy for Data and Safety Monitoring and the National Cancer Institute's Cancer Center Support Grant (CCSG) Data and Safety Monitoring guidelines for NCI-designated Cancer Centers. As described herein, the extent of monitoring will vary by the degree of risk encountered by subjects on a study, the study sponsor, the type of agent(s) involved, and the phase of the trial.

The UICC Data and Safety Monitoring Plan (DSMP) provides a blueprint for the oversight of all clinical trials conducted at the UICC regardless of the trial phase or sponsor type. The DSMP covers all cancer-related clinical trials that have been approved through the UICC Protocol Review Committee (PRC). The DSMP requires that every interventional study submitted to the PRC include a DSMP that is appropriate for its level of risk, which is assigned by the PRC. This helps ensure the safety of participants and the quality, validity, and integrity of the data of these trials. The DSMP also provides for the appropriate and timely suspension or early termination of trials based on efficacy results, unfavorable benefit-to-risk, or inability to answer study questions.

2. Definition of Clinical Trials and Monitoring Requirements for Study Types

2.1 Clinical Trial Definition

The UICC Data Safety and Monitoring Plan (DSMP) has adopted the National Cancer Institute (NCI) policy for Data and Safety Monitoring of Clinical Trials. For the purposes of this plan, UICC uses the National Institutes of Health definition of a clinical trial, which is "clinical research studies involving human participants assigned to an intervention in which the study is designed to evaluate the effect(s) of the intervention on the participant and the effect being evaluated is a health-related biomedical or behavioral outcome."

Participants in clinical trials may be patients with cancer or people without a diagnosis of cancer, but at risk for developing cancer in the future.

With respect to diagnostic research employing tissue and/or body fluids, 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 of the study subject. Such

information may impact some aspect of the study's outcome, and the assessment of this impact may be a key goal of the trial. In contrast, tissue and body fluid studies thatdo not use the resulting information in any manner that can affect the outcome of studysubjects are not clinical trials and are NOT covered by this policy (unless gathering thetissue or body fluids itself imposes additional risk on study subjects).

For diagnostic research utilizing 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 of the study subject. This information may impact some aspects of the study's outcome and the assessment of this impact may be a key goal of the trial. In contrast, studies that do not use this information in any manner that can affect the outcome of study subjects are not clinical trials and are NOT covered by this policy (unless performing the diagnostic test itself imposes some risk on study subjects). These are studies in which the only objective is gathering data on the characteristics of a new diagnostic approach.

Behavioral clinical trials test interventions aimed at eliminating or reducing human activities associated with enhanced cancer risk (e.g. tobacco use, poor nutrition, and sun exposure), or eliminating or reducing morbidity associated with cancer screening, diagnosis, and treatment. In contrast, studies that do not test interventions are considered observational and are not clinical trials.

2.2 Monitoring Requirements by Study Type

All interventional clinical trials are required to submit a study specific DSMP to the PRC with the initial submission for the study. If the study is a phase III investigator initiated therapeutic clinical trial, the DSMP needs to include plans for an independent Data and Safety Monitoring Board (DSMB). As part of the initial review, the PRC reviews the study specific DSMP to assure it is appropriate for the study (see PRC below and Protocol Review and Monitoring System Protocol Review Committee (PRC) Policies & Procedures in Appendix 6).

2.2.1 Externally Monitored Studies

If a study is already being monitored by a data and safety monitoring committee that has been formed by a national cooperative group, a pharmaceutical sponsor, a study-specific Data and Safety Monitoring Board (DSMB) for a Phase III trial, or the Data and Safety Monitoring Committee of another Cancer Center that is NCI Designated, then the UICC Data and Safety Monitoring Committee (DSMC) does not actively monitor the study. These protocols will be monitored as follows:

a. Studies Monitored by A DSMB

Multicenter/Phase III studies are required by the FDA and NIH to be monitored by an independent DSMB.

b. National Clinical Trials Network (NCTN)

Clinical trials by the NCTN are monitored based on established group practices for data submission, reporting, review, and monitoring.

c. Industry Trials

Trials sponsored by the pharmaceutical industry are monitored based on the sponsor's established practices for data submission, reporting, and review and monitoring as described in the protocol.

d. NCI Designated Cancer Center Oversight

At the discretion of the DSMC Chair, multi-site institutional trials conducted at another Cancer Center with NCI Designation may be monitored by that Cancer Center's Data and Safety Monitoring Committee according to their NCI approved DSMP. Documentation of review by the external DSMC demonstrating adequate data and safety monitoring must be on file with the UICC DSMC.

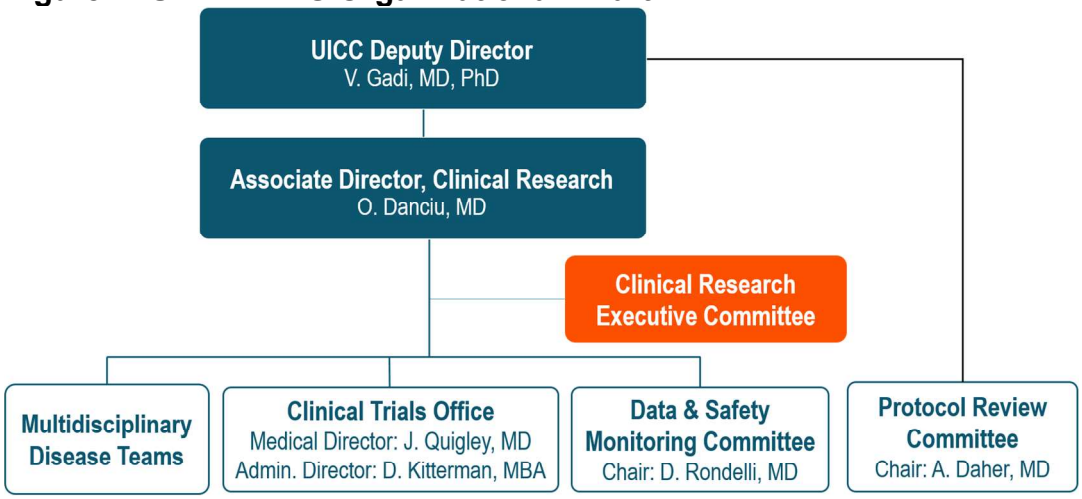
2.2.2 UICC-Monitored Studies

If a study is UICC investigator-initiated, and not monitored by an independent DSMB or another DSMC at an NCI Designated Cancer Center, then it will adhere to the policies and processes described in this plan and the UICC DSMC will serve as the protocol's DSMC and will adhere to the policies and processes described in the DSMP. If the study is an investigator-initiated trial from an external institution, then the sponsoring institution's DSMC will be responsible for monitoring the study.

3. Clinical Research Committee Structures and Relationships

The UICC Director and Associate Director for Clinical Research bear the ultimate responsibility for the conduct of cancer clinical research at UICC, including data and safety monitoring. This responsibility is shared with the various offices and committees that they oversee and appoint. Below is a summary of the individuals and bodies involved in the UICC Clinical Research Program, and their respective roles and responsibilities in data and safety monitoring. The Protocol Review and Monitoring System (PRMS) leadership structure is depicted in Figure 1.

Figure 1: UICC PRMS Organizational Chart



3.1 Principal Investigator of Individual Clinical Trials

3.1.1 Role

The UICC Director and Associate Director for Clinical Research hold the designated local PI responsible for the conduct of the study and for the data and safety monitoring for his/her clinical trial, including those trials conducted across multiple sites. All PIs are subject to the UICC policies regarding the conduct of cancer clinical research. The UICC PI is responsible for the design, conduct, analysis, and dissemination of each protocol. The PI also is expected to monitor the conduct of the study, including data and safety, from activation to study completion. The PI is responsible for assuring that the protocol has a DSMP and that procedures are in place for appropriate implementation.

3.1.2 Investigator-Sponsor Responsibilities

The PI is responsible for:

1. Developing a protocol with an appropriate DSMP and consent form and submitting for review and approval to PRC and IRB in accordance with institutional policy.

2. Constituting a DSMB, if needed, prior to activation.

3. Creating a structured adverse event determination and monitoring and reporting system, including standardized forms and processes for treating or referring patients with adverse events.

4. Notifying the PRC when there are substantive changes in the scientific merit of protocols.

5. Submitting protocol amendments in a timely manner to applicable committees/boards.

6. Providing complete, accurate, and timely data and safety monitoring reports.

7. Reporting adverse events, serious adverse events, unanticipated problems, and protocol deviations as required to applicable agencies and committees/boards.

8. Presenting and publishing results and reporting these to the IRB.

3.1.3 Education and Training Requirements

Every UICC investigator is required to successfully complete Human Subjects Research (HSR) and Good Clinical Practice (GCP) Collaborative Institutional Training Initiative (CITI) training modules. The courses must be completed and renewed every three years. Investigators keep up to date on the latest rules and regulations regarding the design and conduct of research involving human subjects through the UIC IRB website and through training provided by the CTO.

3.2 UICC Clinical Trials Office (CTO)

The UICC Clinical Trials Office (CTO) serves as the UICC's Clinical Protocol and Data Monitoring resource (CPDM). The CTO provides the centralized administration coordination, management, education, policies and procedures, and ongoing support to all UICC clinical research coordinator and to those committees which conduct scientific review and accrual monitoring, provide data and safety monitoring, and ensure adherence to UICC, institutional, state, and federal regulations. The CTO works closely with the Associate Director for Clinical Research to assure that there is sufficient staffing to meet the current and anticipated needs of the clinical research program at UICC.

The CTO reports directly to the Associate Director of Clinical Research. Its role is to foster an effective and efficient clinical research infrastructure. The office provides all necessary resources, staffing, informatics, and processes required to support the development, activation, and conduct of protocols, and quality assurance, through protocol close-out, under a single, centralized organizational structure.

3.3 Disease Teams

UICC Disease Teams oversee the clinical trials activities conducted within disease groups. Disease Team leaders are appointed by and report to the Associate Director for Clinical Research. Each is responsible for the ensuring the overall effectiveness of their respective disease team.

Disease Teams (DTs) are responsible for the overall quality and conduct of protocols in their portfolio. In this role, teams evaluate proposed clinical trials at least monthly. This includes assessing the protocol's scientific merit, accrual feasibility based on an assessment of fit with UICC's patient population and clinical feasibility based upon UIC clinical practices, the ability of the trial to fill gaps in the clinical trial portfolio for particular patient populations, overlap with existing studies or competing clinical trials that are ongoing, and the alignment of the study with the mission of the UICC.

Regardless of type of sponsor, all new cancer-related studies enrolling UIC cancer patients are to be reviewed and endorsed by the relevant UICC DT before they can be submitted to the Protocol Review Committee. The DSMB will communicate with the Disease Teams as needed and will inform Disease Team of any issues or concerns that may impact the Disease Team's clinical trial portfolio.

3.4 Protocol Review Committee (PRC)

The Protocol Review Committee serves as the scientific review and monitoring body for all UICC new and enrolling protocols. The role of the PRC is to assure that only those trials that are scientifically meritorious, statistically sound, have a high probability of completion within a reasonable timeframe, and meet the scientific mission and goals of UICC are approved and activated.

The PRC is composed of faculty from the basic sciences, clinical sciences, and population and control sciences (see PRC roster, Appendix 4). The PRC Chair is appointed by the Cancer Center Director and the Associate Director of Clinical Research with the endorsement of the UICC Clinical Research Executive Committee. Voting faculty members represent a diverse range of clinical research disciplines, including medical, surgical and radiation oncology, and biostatistics. The goal is to have a balance of senior and junior faculty and representatives from needed specialties to provide high quality, scientific review ofprotocols. The PRC meets twice a month. No PRC meeting may commence with the review of new protocols unless quorum of voting faculty is reached (>50% of committee membership, including the PRC Chair or Vice Chair and one biostatistician member). Day-to-day support of the PRC is provided by the PRC Committee Manager, who is administratively basedin the CTO.

The PRC will not accept an interventional study for review if it does not have a DSMP. The presence of a plan is confirmed by PRC staff prior to placing the protocol on the PRC agenda.

A PRC member who is the PI of a study being reviewed at a PRC meeting must be recused from the meeting during the review, discussion, and voting on the protocol. A PRC member who is a Co-Investigator of a study being reviewed at a PRC meeting is allowed to be present for discussion, however he or she must abstain from voting. A PRC member that has a financial conflict with a study being reviewed at a PRC meeting

must be recused from the meeting during the review, discussion and voting on the protocol. The primary reviewer presents the protocol during the PRC meeting, and discussion ensues. The PRC approves the protocol and DSMP. For UICC investigator-initiated studies, the PRC also assigns a risk category. The risk level is used to determine the frequency and type of monitoring/auditing. Only protocols approved or exempted by the PRC can be submitted to the IRB.

Once a protocol is activated, the PRC is also responsible for monitoring the scientific progress of the clinical protocol. This occurs at least annually. Additionally, amendments that change any of the following must be submitted for review and approval by PRC: study rationale, response criteria, eligibility criteria, objectives, study design, treatment plan, sample size, stopping rules, or statistical plan. The PRC has ultimate authority to suspend or close a trial for issues related to scientific merit. The PRC is also responsible for monitoring accrual to all interventional hypothesis-driven cancer trials beginning six months after a protocol opens. The PRC has a policy for monitoring trial accrual and a process for closing low accruing trials (Appendix 6).

The PRC and IRB have complementary yet non-overlapping roles in the review, approval and monitoring of cancer clinical protocols conducted by the UICC. As the PRC focuses on scientific review, the IRB focuses on ethical conduct and patient safety. Similarly, the PRC has a complementary but not duplicative role with the DSMC, although there is appropriate communication and collaboration among these bodies relative to their scope.

3.5 Institutional Review Board (IRB)

The human research protection program at University of Illinois, Chicago (UIC) is fully accredited by the Association for Accreditation of Human Research Protection Program (AAHRPP). The UIC IRB or external IRB reviews all research involving human subjects conducted by UIC faculty, staff, and students. The IRB of record assures that research adheres to the highest ethical standards and is conducted in accordance with federal, state, and institutional regulations. As such, the IRB has primary responsibility for the protection of the welfare of human subjects participating in human subject research. The major work of the IRB consists of the assessment of research related benefit-risk ratios and assuring that informed consent is properly obtained and documented. The IRB has full authority to approve, require modifications prior to final approval, disapprove, suspend, or terminate for cause all research activities that fall within its jurisdiction. The IRB also has a responsibility to society in general, and to the UIC community in particular, to review and approve worthwhile studies in a timely fashion.

It is an institutional policy that the IRB will not review any cancer study until it has been reviewed and approved by the PRC, or deemed exempt from PRC review. In addition to the PRC, the UIC IRB reviews the clinical trial DSMP in each study to ensure that it is appropriate for that specific trial.

3.6 Data and Safety Monitoring Committee (DSMC)

Once studies are IRB approved and activated, the DSMC is charged with reviewing all investigator initiated, interventional UICC clinical trials. In regards to the relationship that the DSMC has with other persons and committees outlined above, DSMC review outcomes and audits are distributed to the study PI, as well as the IRB with the continuing review. The details of the DSMC are described extensively in a later section of this document.

4. Data and Safety Monitoring Policies and Processes

Below is a summary of the process of review and activation, monitoring, reporting, and outcome decisions for UICC protocols. This process shows the responsibility, inter-relationships and interactions of UICC clinical research bodies to assure the appropriate levels of review, approval monitoring, and closure of protocols.

4.1 Protocol Review and Activation Process

Below are the steps in protocol development, activation, and monitoring, along with individuals or bodies tasked with each of these steps.

1. ***Protocol Development and Identification***: UICC investigators develop innovative protocols based on clinical experience and translational research, or identify a suitable protocol based on the UICC patient base.

2. ***Disease Team Review*****:** As previously stated in the Disease Team (DT) section 3.3.

3. ***Protocol Review Committee and Approval***: Previously defined in the Protocol Review Committee section 3.4.

4. ***IRB Review and Approval***: Previously stated in section 3.5.

5. ***Activation*****:** Studies approved by the IRB are readied for activation. This step includes site initiation visits and confirmation of the availability of drug. Budget and contract negotiations for externally funded studies occur simultaneous with the above reviews, and must be completed prior to trial activation. The CTO is responsible for 'activating' the protocol in the clinical trials management system, OnCore, and assuring that study is listed on clinicaltrials.gov.

4.2. Protocol Monitoring Processes

1. ***Subject Registration:*** The UICC tracks and reports all subjects who enroll in

cancer-related clinical trials in the clinical trials management system, OnCore. Investigators, with the support of their research coordinators or the CTO, are responsible for subject registration. The PI has overall responsibility for ensuring patient eligibility in accordance with protocol criteria. The Clinical Research Coordinator (CRC) provides a crosscheck to ensure compliance with eligibility criteria. Once the investigator signs the consent document and crosschecking is complete, the CRC enrolls the subject in OnCore.

2. ***Data and Safety Monitoring***: The principal investigator is ultimately responsible for the data and safety monitoring of the trial and shall ensure that reportable serious adverse events and other unanticipated problems are reported to the IRB and other bodies as required within the appropriate timeframe per CTO SOP SCON12 AE-SAE Documentation & Reporting (Appendix 7). For investigator initiated interventional trials, the PI reports a summary of all trial activities, including AE/SAEs (defined in section 7.1), to the DSMC for review at the timeframe indicated by the risklevel assigned by the PRC.

   DSMC monitors UICC initiated studies in accordance with the identified risk level and decides whether a study should be continued based on criteria outlined in DSMP. This recommendation is communicated to the PRC.

3. ***Scientific Progress Review***: The PRC is responsible for the ongoing scientific review of all UICC studies. A determination of whether there have been changes in the scientific merit occurs at least annually through the continuing review process. PI must submit annual progress reports to the PRC for all open to accrual clinical trials. The monitoring of accrual occurs more frequently and in accordance with the accrual monitoring policy of the PRC. The goal is to terminate low accruing trials that will not realize their accrual targets within a realistic timeframe.

   The PRC determines whether a study should be allowed to continue based on accrual and scientific integrity of the study. Its determination to terminate a protocol is reported to the IRB.

4. ***Annual IRB Review***: All UICC investigators are required to submit an application to the IRB for continuing review each year. The submission includes the data and safety monitoring reports received by the investigator, information on accrual, a summary of adverse events, publications based on study findings, and publications within the scientific community that may affect the outcome of the current trial.

   The continuing renewal application is reviewed by the IRB and a determination is made as to whether the study should be continued based on a review of all materials and other information that may have been submitted to the IRB in the form of amendments. A letter is sent to the UICC investigator notifying him/her of

the recommended action with a copy sent to the CRC or CTO for inclusion in the study file. If the IRB determines that a study should not be allowed to continue based on the DSMC report and/or the audit of data, the IRB immediately notifies the UICC investigator that the study has been closed (or suspended until the necessary amendments are submitted and approved by the IRB as required).

Any determination by the IRB due to safety or non-compliance issues that results in temporary or permanent suspension of an NCI-funded clinical trial shall be reported by the IRB to the NCI grant program director responsible for funding the trial, and other appropriate agencies, with a copy of the communication to the principal investigator. These closures will be reported to the NCI Program Director within 10 working days of the determination.

5. ***Reporting:*** The actions taken by the DSMC, PRC, or IRB, are communicated in writing to the investigator. The investigator is responsible for complying with any required actions and providing a timely response, as required.

   Reports of study non-compliance, closure, or suspension are also sent to the Associate Director for Clinical Research.

   The Committee Chairs and/or the Associate Director for Clinical Research are responsible for verifying that the investigator has complied with the recommended action.

4.3 Requirements for Submission of Monitoring Plan

Every interventional UICC protocol must include a plan for data and safety monitoring. The PRC will not accept an interventional protocol for review unless it has a monitoring plan.

The requirements for externally monitored trials were previously described in section 2.2.1. The requirement for UICC investigator-initiated pilot, phase I and phase II studies are that they are reviewed by the DSMC as described below. The requirement for Phase III studies is that they will be reviewed by an independent DSMB, as described in the study DSMP, which will list the Chair and the members of the DSMB.

4.4 Determination of Risk

Each UICC investigator-initiated trial undergoes scientific review by the PRC, in part, to ensure that procedures are in place to ensure the safety of subjects depending on the degree of risk of the study. The PRC assigns a category of risk to every UICC interventional study and the DSMC follows the plan of review for that category.

The purpose of assigning a level of risk (low, moderate, or high) to an UICC

investigator-initiated trial is to ensure that data and safety monitoring activities are appropriate for the level of subject risk. In order to make a decision, the PRC reviews the following criteria:

- Expected duration of the study based on the study design and estimated rate of enrollment.
- Whether the study is multicenter
- Study population (e.g. children, pregnant women).
- Procedures to ensure the safety of subjects in accordance with the degree of risk.
- Methods to ensure the validity and integrity of the data, including an adequate biostatistical design and appropriate data analysis.
- Adequate data management systems including case report form records and a plan for data collection.
- Procedures for reporting serious adverse events to the appropriate departments/committees (e.g. IRB, FDA, NIH).

The risk level determines the frequency of monitoring for a protocol, which may be altered (i.e., increased) if issues arise.

4.5 Definition of Risk Levels

There are three levels of risk that may be assigned: High, Moderate and Low. Each category is described below.

High Risk
Studies assigned to the high-risk category include any therapeutic investigator-initiated pilot, phase I, II, or trials involving IND/IDEs, investigator-initiated multi-center trials, as well as any research involving recombinant DNA molecules (gene transfer) and cell-based therapies. These clinical trials will be reviewed on a quarterly basis by the DSMC.

Moderate Risk
Studies assigned to the moderate-risk category include most investigator-initiated, single center, Phase I or II trials using FDA-approved, commercially available compounds. Moderate Risk trials will be reviewed biannually (every 6 months) by the DMSC.

Low Risk
Studies assigned to the low-risk category include investigator initiated non-therapeutic

trials. Low risk trials will be reviewed annually by the DSMC.

Investigator initiated phase III trials will also be reviewed by a study specific DSMB at timeframes specified in their approved DSMP.

4.6 Determination of Monitoring Frequency Based on Risk Assignment

The level of monitoring is dependent on the type of study and the level of monitoring conducted by an outside entity. For investigator-initiated interventional studies, the PRC will assign the risk level and this will determine the frequency of monitoring per the DSMP risk-monitoring policy. Once the protocol is approved and the risk is assigned by the PRC, then the DSMC follows the plan, making adjustments in frequency (i.e., increased monitoring) if and as needed over the course of the trial conduct.

The method and level of monitoring will correspond with the degree of risk involved in participation and the size and complexity of the study.

The CTO QA Specialist will monitor participant research charts on a quarterly basis and communicate audit results to the DSMC for review, per below:

Type of Trial	% of cases audited
UICC Investigator Initiated Interventional Therapeutic	50%
UICC Investigator Initiated Interventional Non-Therapeutic	10%

Above is the minimum percentage of charts, however if a major trend is identified, more charts will be reviewed.

5. UICC Data and Safety Monitoring Committee Role and Responsibilities

5.1 Role

The UICC Data and Safety Monitoring Committee (DSMC) serves as the body directly responsible for the data and safety monitoring of approved and activated UICC investigator-initiated interventional trials. DSMC serves as the Data and Safety Monitoring Board (DSMB) for UICC-approved cancer protocols that require, but lack, an external DSMB. The DSMC is a multidisciplinary committee that provides independent oversight of clinical trials conducted at UICC. The Committee is specifically charged with monitoring of safety of participants in cancer clinical trials, and the conduct and progress of the trial for all interventional investigator initiated cancer clinical trials at the UICC. The DSMC's efforts to assure patient safety in this regard complement those of other UICC offices and committees engaged in fostering and overseeing the conduct and compliance of these trials. The DSMC ensures effective communication,

collaboration, awareness and compliance with federal, state, CCSG and institutional requirements as it relates to data and safety monitoring. The DSMC's roles include but are not limited to:

1. Initial review of newly opened protocols, or changes in protocol (including but not limited to: accrual, toxicity and efficacy analysis, statistical rules for dose escalation or cohort expansion) requiring DSMB review
2. Ongoing study monitoring: including accrual, reported adverse events, compliance issues (including major protocol deviations)
3. Consider factors external to study when relevant information becomes available, such as scientific or therapeutic developments which may have an impact on the safety of the participants or ethics of the study
4. Review of CTO QA audit findings and action plans (corrective and preventive) relating to data integrity or patient safety
5. Safety review: SAE and including all reportable adverse events
6. DLT review
7. FDA IND report review for PI held INDs
8. Recommend early termination based on efficacy results
9. Recommend termination due to unfavorable benefit-to-risk or inability to answer study questions
10. Recommend continuation of ongoing studies
11. Approve dose escalation or cohort expansion
12. Consideration of overall picture; primary and secondary analysis
13. Modify sample sizes based on ongoing assessment of event rates

5.2 Authority

The DSMC has the authority to require amendments to a protocol, suspend a protocol, or recommend termination of a trial within its jurisdiction for data integrity and patient safety reasons.

Based on the DSMC committee vote, the DSMC may suspend a trial or recommend termination to the IRB for safety and ethical reasons, or may refer scientific merit concerns to the PRC for follow-up. The DSMC may also institute other appropriate conditions needed for subject safety. As an example, if a trial has been deemed high risk and the DSMC would like monthly meetings with the PI this can be mandated or if the PRC has flagged an inadequate DSMB from a pharmaceutical company they can request that the DSMC have a regular review of the study.

5.3 Responsibilities

The DSMC is charged with reviewing all institutional cancer related prospective studies involving human subjects designed to answer specific questions about the effect or

impact of particular biomedical research or behavioral interventions; these interventions may include drugs, treatments, procedures, devices, or behavioral or nutritional strategies. Participants in clinical trials may be patients with cancer or people without a diagnosis of cancer, but at risk for developing cancer in the future. It is recognized that clinical trials sponsored by NCI, NCTN, and industry are continually monitored for compliance by external parties. However, institutional clinical trials without outside sponsorship are not audited and are the focus of the monitoring system described here.

The types of trials covered under the scope of the DSMC are:

1. An *investigator-initiated* (sometimes referred to as *institutional*) clinical trial is defined for the purposes of these guidelines as a clinical research study authored by a member of the UIC faculty or staff. Such studies are not primarily sponsored or subject to scientific review or monitoring by an outside agency (e.g. industry, cooperative group, NCI, NIH, FDA, or other institution). Although an investigator may obtain investigational drugs and/or funding from an outside agency or industry in support of the research, if the clinical trial is not subject to monitoring by that agency it is categorized as an investigator-initiated clinical trial and internally monitored by the DSMC.

2. Any study that a UIC Principal Investigator is collaborating/participating in that does not have an adequate DSMP as determined by the PRC.

The types of trials not covered by the DSMC are:

1. Phase III investigator initiated therapeutic interventional clinical trials involving significant risk are reviewed by Independent Data and Safety Monitoring Boards (DSMBs) established by the Principal Investigator and supported through the funding agency. The study specific DSMP containing plans for the study's DSMB is reviewed for appropriateness by the PRC. Individuals who are invited to become members of the Independent DSMB should identify any perceived or real conflicts of interests, and these should be considered before formal appointment. Study specific DSMB reports are provided to the DSMC.

2. Externally sponsored investigator initiated trials. This type of investigator initiated trial will follow its own institution's DSMP. That institution will be the one responsible for monitoring of the trial.

5.4 Membership Composition of the DSMC

The DSMC includes representation from the following groups: the Department of Pharmacy, Department of Biostatistics, UICC members involved in clinical research, other UIC faculty who provide relevant expertise, and the UICC CTO (see Appendix 5, DSMC Membership Roster).

Current voting members include:

1. The DSMC Chair
2. The DSMC Vice Chair
3. Pharmacy representative
4. Biostatistician representative
5. UICC members with representation from Medical oncology (including neuro-oncology), surgery, radiology, radiation oncology, and nursing

Non-voting attendees include:

1. QA Specialist
2. DSMC Personnel
3. CTO Clinical Research Manager or CRC

5.5 Membership Appointments

The DSMC Chair and Vice Chair are identified by the Associate Director of Clinical Research and presented for review and approval by the Cancer Center Director. Potential DSMC members are identified by Associate Director for Clinical Research and the DSMC Chair and Vice Chair and presented for review and approval by the Cancer Center Director. Membership from the groups listed above ensures appropriate representation and communication with those groups that share responsibility for patient/participant safety issues related to UICC trials.

Members are appointed for three years, which is renewable annually by mutual consent with a two-term limit subject to extension by the Associate Director for Clinical Research. Ad hoc members may be appointed by the Chair, as needed.

5.6 Member Responsibilities

The members of the DSMC are expected to be familiar with protocols being reviewed. Members are also expected to be familiar with scientific and therapeutic advances as they relate to the protocols being reviewed. Members are expected at a minimum to attend 10 of 12, or 85%, of regularly scheduled meetings. The DSMC Administrator trains all new members on the review process, and provides them with a copy of the DSMC Policy outlining their responsibilities. New members are then trained on how to conduct data and safety monitoring reviews by the DSMC Chair.

Each study will be assigned a primary and secondary Medical Monitor. Medical Monitors are responsible for reviewing all adverse events (in addition to unexpected adverse events), safety data, efficacy data, and protocol deviations in the ongoing clinical trial at each new dose level prior to dose escalation. It is important to note that the Medical Monitor reviews all SAEs and major protocol deviations reported on their assigned studies in real time. The Medical Monitor also provides a summary of his/her

review to the DSMC for review prior to the DSMC meeting, and makes recommendations to the DSMC during the meeting. Secondary Medical Monitors will be responsible for reviewing all adverse events (in addition to unexpected adverse events), safety data, and protocol deviations in the ongoing clinical trial at each new dose level prior to dose escalation. If the primary Medical Monitor is unavailable for study review, the secondary Medical Monitor will serve as the primary Medical Monitor in the interim.

A Biostatistician should provide suggested formats or templates for data presentation including efficacy reporting for the initial meeting of the DSMC for initial study presentation. The Biostatistician will also be responsible for reviewing all adverse events (in addition to unexpected adverse events), safety data, efficacy data, and protocol deviations in the ongoing clinical trial at each new dose level prior to dose escalation. The Biostatistician is responsible for making appropriate statistical recommendations regarding the ongoing design of the study, and presenting quarterly efficacy reports for review.

5.7 Conflict of Interest

UICC DSMC members are subject to the UIC and UICC policies regarding standards ofconduct and conflict of interest. Individuals who are invited to be voting members, non- voting members, or attendees of DSMC meetings must disclose any potential or real conflict, including financial terms, to the Chair and the relevant UICC official prior to accepting a position. Decisions relative to conflict of interest are to be made based on institutional policy (see Appendix 11, The University of Illinois System Policy on Financial Conflicts of Interest in Research).

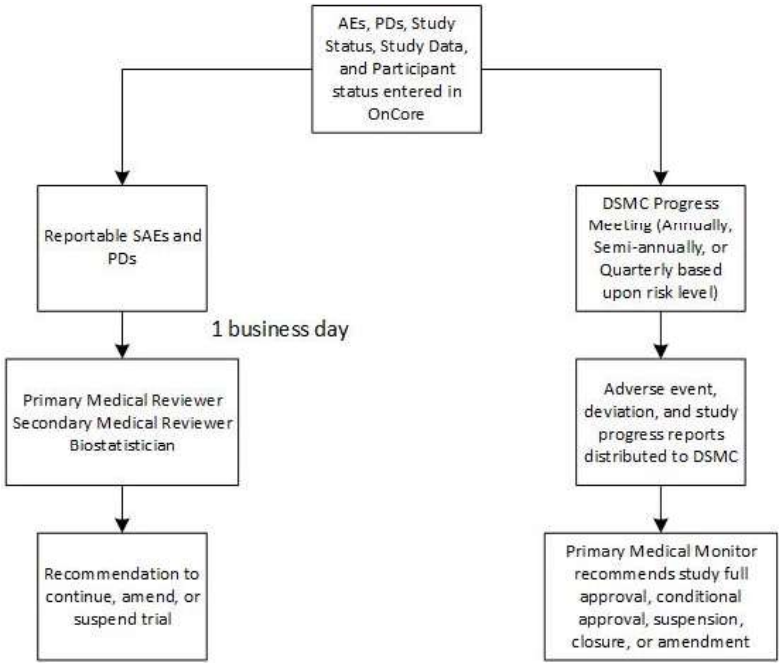
No one who has a direct or indirect relationship with the study under review is allowed to serve as a Medical Monitor (see description below). In addition, the PI is asked to disclose any conflicts of interest prior to each meeting and is not allowed to be present during DSMC deliberations or cast a vote if they are a research team member of the study being reviewed or if they have a conflict of interest due to a relationship with the sponsor, intellectual property ownership with study investigators, or personal financial investments related to the study or study sponsor. Co-investigators are allowed to be present during discussion but must abstain from voting. In addition, members of the DSMC may not serve simultaneously on the IRB, the PRC, or as Clinical Trials Office Medical Director or Associate Director of Clinical Research.

5.8 DSMC Personnel

The DSMC Personnel provides administrative support to the DSMC Chair, Vice Chair and committee. The DSMC Personnel prepares the meeting packet and informs the Committee with any updates. These include studies in progress and other information to facilitate the committee's ongoing review of protocols. The personnel maintains and distributes the meeting minutes from the DSMC. The minutes include attendance, quorum, conflict of interest, study title, review comments, votes and outcome of the trial review.

5.9 DSMC Monitoring Process

Figure 2: DSMC Monitoring Process



The monitoring process is as follows (overview shown in Figure 2):

1. Each protocol is assigned to a primary and secondary Medical Monitor and a Biostatistician. This is a physician or another qualified member of the DSMC who has expertise in the therapeutic area of the protocol and is not directly involved in this trial. The Medical Monitor is responsible for reviewing all adverse events (in addition to unexpected adverse events), safety data, and activity data observed in the ongoing clinical trial at each new dose level prior to dose escalation. The Medical Monitor also provides a summary of his/her review to the DSMC for review prior to the DSMC meeting. It is important to note that the Medical Monitor reviews all SAEs and major protocol deviations reported on their assigned studies in real time.

2. The PI, or their designee, is responsible for entering all adverse experiences and protocol deviations into OnCore to allow for reporting to the DSMC of all AE/SAEs, safety and toxicity data, and protocol deviations that have occurred for review at the frequency specified by the risk level assigned to the study.

3. The summary of all adverse events and protocol deviations are submitted to the DSMC, and these reports are reviewed during the DSMC meetings that take place per the frequency specified by the study's risk level. Participants are only

identified by initials and no other personal health information (PHI) is included in the reports.

The Medical Monitor may recommend reporting adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial based on their review of AE/SAE data and protocol deviations observed throughout the life of a clinical trial. In such circumstances, an ad hoc DSMC meeting will be convened to discuss corrective actions with the PI.

PIs can appeal any DSMC decision by submitting a written request for an additional review to the DSMC. However, there is no appeal process beyond the DSMC and thefinal DSMC decision cannot be overturned.

5.10 Meeting Frequency

The DSMC meets monthly to review the all active research protocols under DSMC purview. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC meets (by conference call or in person) within one business day following the notification of an unexpected serious adverse event felt to be related to the study treatment (see section 7, Serious Adverse Event Reporting).

5.11 Meeting Format

For DSMC meetings, the DSMC personnel is responsible for meeting preparations under the direction of the Chair and for preparing the DSMC meeting packet, which includes an agenda, minutes from the prior meeting, a list of current internally-reviewed IITs, applicable PI study reports, and any other pertinent information to be discussed. Also in the meeting packet, which is sent to members at least one business day in advance, are copies of all reported AEs, SAEs, and major protocol deviations during the reporting period for each clinical trial under review. The PI may be asked to provide a detailed and comprehensive narrative assessment of current adverse events to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. DSMC members are provided with the principal investigator's assessment in a report summarizing adverse events, safety data, and activity data observed during the specified time period described in each protocol.

Before commencing each meeting, members are reminded that meeting proceedings areconfidential and any conflicts of interest are noted in the meeting minutes. The DSMC Personnel confirms that the meeting has a quorum. Quorum for DSMC meetings is defined by having >50% of voting members in attendance in person or via conference call. Final decisions will not be made without appropriate representation.

New UICC investigator initiated interventional studies are assigned a primary and secondary Medical Monitor by the DSMC Chair or Vice Chair. Medical Monitors receive SAE reports within 1 business day of the study team becoming aware of the event. Medical monitors are responsible for reviewing all reported information as submitted to the DSMC meeting, and in turn completing a Medical Monitor Report (see attached template) for inclusion in the DSMC meeting packet. During the meeting, the Medical Monitor leads a discussion on the general conduct of the trial, a review of outcome results (toxicity and adverse events). The Medical Monitor for the specific trial makes a recommendation (full approval, conditional approval, suspension, closure, including recommendation about amendments), and then voting members vote on the status of each study.

A summary of the committee's determination and findings are sent after the meeting within 5 business days to each investigator and his/her study team, as well as the PRC, for submission by the study team to the UIC IRB.

In its notification to the PI, the DSMC provides the rationale for its determination. It may also include recommendations/requirements that will lead to improved participant safety and/or efficacy, significant benefits or risks that have developed, or other changes determined to be necessary. The DSMC determination and rationale are included in the continuing review application submitted to the UIC IRB.

Should the DSMC take note of slow accrual or lack of scientific progress during its review of a protocol, it will refer such matters to the PRC for appropriate review.

Type of DSMC Meeting	Frequency	Outcomes
Regular DSMC Meeting	Quarterly	- Full Approval - Conditional Approval - Suspension - Closure
Ad Hoc DSMC Meeting	As Needed	- Full Approval - Conditional Approval - Suspension - Closure
Dose Escalation/Cohort Expansion	Per Protocol	- Full Approval - Conditional Approval - Suspension - Closure

5.12 Frequency of Trial Review

All UICC Investigator-initiated studies require continuous monitoring by the PI of the study. However, the determination of how often a study will be reviewed at a DSMC meeting is dependent of its level of risk that was assigned by the PRC. Routine reviews will be performed until the study closes to accrual, and the DSMC will review SAE and

PD reports until the study is closed to IRB review.

Level of Risk	Frequency of DSMC Review
Low Risk	Once a year
Moderate Risk	Every 6 months
High Risk	Quarterly

RISK CATEGORY	STUDY PROJECT CHARACTERISTICS	UICC DSMC STUDY PROGRESS REPORTING REQUIRED? [1]	UICC DSMC AUDIT FREQUENCY[1]
Low	- Investigator initiated non-therapeutictrials.	Annually	Quarterly
Moderate	- Investigator-initiated, single center, Phase I or II trials using FDA-approved,commercially available compounds.	Semi-Annually	Quarterly
High	- Therapeutic investigator-initiated Pilot,Phase I, II, or trials involving IND/IDEs - Investigator-initiated multi-center trials - Research involving recombinant DNA molecules (gene transfer) and cell-based therapies	Quarterly	Quarterly

1 Time points are based from the date of trial activation.

5.13 DSMC Dose Escalation/Expansion Approval Meeting

Prior to proceeding to the next dose cohort or expanding the current cohort the PI must get DSMC Medical Monitor approval, with input from the DSMC Chair or Vice Chair and DSMC Biostatistician. The procedure for obtaining approval is as follows:

- The PI or their designate must contact the DSMC Personnel to inform them that they would like to expand the current cohort or proceed to the next cohort.

- OnCore, UICC's clinical trial management system, is utilized to collect data for all investigator initiated therapeutic clinical trials. The DSMC Personnel will run a report of toxicities and efficacy for subjects in the current cohort, and for all patients on study, and provide it to the Biostatistician and Medical Monitor for the

study.

- The DSMC Personnel will inform the Medical Monitor and Biostatistician of the specific trial that the PI is seeking a dose escalation or cohort expansion (whichever is applicable). At that time, the DSMC Personnel will begin working with study team to coordinate a meeting within 5 business days of the PI request.

- The Medical Monitor, DSMC Chair or Vice Chair, Biostatistician, PI and the DSMC Personnel (or designee) must be present at the meeting.

- Once the meeting has been held, the DSMC Personnel will draft the decision letter (approval/disapproval), and this will be forwarded to the PI.

- Dose Escalation and/or Cohort Expansion cannot begin prior to approval being granted at the meeting with the Medical Monitor.

- The DSMC Decision Letter must be maintained in the regulatory files and sent to the IRB at the time of Continuing Review.

- PIs can appeal any DSMC decision by submitting a written request for an additional review to the DSMC. However, there is no appeal process beyond theDSMC and the final DSMC decision cannot be overturned.

5.14 Reporting of DSMC Outcomes to the IRB

The summary of all discussions of adverse events are included in the UICC investigator's reports to the UIC IRB as part of its annual progress report.

6. Individual Data and Safety Monitoring Boards

An individual DSMB is to be formed if the study is an interventional investigator initiated randomized Phase III trial. Members are selected by the PI and should largely be comprised of individuals that are not affiliated with UICC or UIC. Members will be selected for the knowledge of clinical research and may include clinical investigators, biostatisticians, other scientists and lay individuals who are familiar with clinical research methodology.

The DSMP outlined in the Phase III UICC investigator-initiated trial is reviewed by the PRC and IRB as part of the protocol submission and review process. The plan will include a description of the reporting mechanisms of adverse events to the IRB, the FDA, and, if applicable, the NIH. The plan is also expected to reflect the IRB's requirements for reporting serious adverse events occurring at UIC and off-site locations.

Individuals who are invited to be members of the Independent DSMB must disclose any potential or real conflict, including financial terms, to the PI and the relevant UICC official prior to accepting a position. Potential conflicts that develop during a member's tenure must be disclosed in a similar manner. Decisions relative to conflict of interest are to be made based on institutional policy.

The protocol-specific, independent DSMB reports its findings and recommendations to the DSMC. The DSMC reviews the report and makes a final recommendation to the UIC IRB, or to the PRC for scientific merit and progress-relevant matters.

Recording and reporting requirements for Phase III trials include:

1. All AEs/SAEs must be recorded for each subject within the subject's research file.

2. Each event must include grade, relationship, expectation and intervention (if applicable)

3. All AEs/SAEs and protocol deviations must be reported according to the DSMC AE/SAE reporting Guidelines (please see DSMC Reporting Guidelines below), unless otherwise excepted by the DSMC and noted in the approval letter (see AE/SAE Reporting Addendum below).

7. Serious Adverse Event/Adverse Event Reporting for UICC Clinical Trials

7.1 Definition of Serious Adverse Event (SAE)

An SAE is any adverse event occurring at any dose level that:

- Is fatal;
- Is life-threatening (subject is at immediate risk of death as a result of the event);
- Is disabling or incapacitating;
- Requires inpatient hospitalization or prolongs current hospitalization (Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE.);
- Is a persistent or significant disability/ incapacity;
- Is a congenital abnormality in the offspring of a subject who received the drug; or,
- Is an event which, though not included in the above points, may jeopardize the subject or may require intervention to prevent one of the outcomes listed above.

7.2 Reports and Recording

All AEs/SAEs must be recorded for each subject within the subject's research file and in OnCore. In addition, each event must include severity, relationship to intervention,

expectedness and action taken (if applicable) per CTO SOP SCON12 AE-SAE Documentation & Reporting (Attachment 8). Every UICC investigator-initiated interventional protocol includes requirements for the reporting of adverse events based on the current version of the Common Terminology Criteria for Adverse Events (CTCAE). The investigator is required to submit all local, unanticipated, SAEs to the IRB within 5 days and all related unanticipated AEs associated with a greater risk of harm than previously known require a report within 15 days. In addition, if the study is conducted under an IND, unexpected, related and serious adverse events (SAEs) are reported to the Food and Drug Administration (FDA).

For interventional investigator initiated studies reviewed by the DSMC, the investigator is required to submit all unexpected and serious adverse events to the DSMC Medical Monitor, with a copy to the DSMC Chair or Vice Chair, within one business day of becoming aware of the event. All AE/SAEs will be reported to the DSMC as required by the risk level assigned to the study. However, if the Medical Monitor determines corrective action is necessary, an “ad hoc” DSMC meeting will be called. For an unexpected serious adverse event felt to be related to the study treatment, the DSMC will meet (by conference call or in person) within one business day following the notification of the event to review the report. Sites of multi-site investigator initiated trials for which UICC is the lead site are required to enter serious adverse events (SAEs), dose-limiting toxicities and stopping rule events into UICC’s Clinical Trials Management System, OnCore. If subject data is not being collected in UICC’s OnCore system, data reports consistent with the requirements outlined in this DSMP must be provided to the UICC DSMC as requested for review. In addition, clinical trial sites are required to submit SAE reports electronically to the DSMC according the same timeframes as for local SAEs. Reporting requirements for Phase III investigator-initiated studies are described in the study specific DSMP reviewed by the PRC and UIC IRB. For studies with an approved DSMC AE/SAE reporting Addendum reporting exclusions will only reflect those specified in the DSMC decision letter, all others must adhere to the DSMC Reporting Guidelines.

7.3 AE/SAE Reporting Addendum for Investigator Initiated Clinical Trials

A DSMC AE/SAE Addendum is provided on a study specific basis to allow for certain expected SAEs to be excluded from the reporting requirements to the DSMC. The DSMC AE/SAE Addendum is documented in a DSMC approval letter. If a PI receives an approval for an addendum the specific approval letter will detail specific reporting procedures that differ from the DSMC Reporting Guidelines.

The procedure for obtaining an AE/SAE Addendum is as follows:

- The Principal Investigator must provide written documentation addressed to the Medical Monitor for their study and the DSMC Chair or Vice Chair. This documentation must detail the rationale for the requested addendum.

- The rationale should detail the specific events and the applicable grades that the PI is seeking to addend in reference to reporting as per the current DSMC Guidelines.
- This drafted documentation should be forwarded to the DSMC Personnel.
- The DSMC Personnel will then forward all documentation to the Medical Monitor and the DSMC Chair or Vice Chair for review and filed as documentation of the request.
- In order to maintain proper documentation, all questions or communications from the Medical Monitor and DSMC Chair or Vice Chair should be sent in written format (i.e. email) to the DSMC Personnel.
- When both Medical Monitor and DSMC Chair or Vice Chair come to an agreement, this is sent to the DSMC Personnel, who sends the decision out to the DSMC for agreement with the decision.
- All DSMC decisions letters (approval/disapproval) will be prepared by the DSMC Personnel and sent to the PI and the Clinical Research Coordinator for the specific study.
- The DSMC decision (approval/disapproval) letter must be retained in the regulatory file and presented to the IRB at the time of continuing review.
- All reporting procedures will follow the current DSMC Guidelines until an approval is granted.
- The PI will amend the protocol to reflect the approved amended AE/SAE reporting language and submit the amendment through the standard process.
- If an approval is not granted for the requested addendum all AEs/SAEs must be reported following the current DSMC Reporting Guidelines.

8. Protocol Deviation Reporting for UICC Clinical Trials

8.1 Definition of Protocol Deviations (PDs)

A protocol deviation is defined as any deviation, whether accidental, unintentional or intentional, from the IRB-approved protocol that is implemented prior to IRB approval. For the purposes of this policy, deviations are categorized as Major and Minor:

- Major protocol violations are those that cause harm to subjects or others, place them at increased risk of harm, impact the scientific integrity of the research, compromise the human subject protection program, have the potential to recur or represent possible serious or continuing non-compliance Major protocol violations may represent an unanticipated problem (particularly when unintentional) and/or potential serious noncompliance and require prompt reporting.
- Minor protocol violations are those not meeting at least one of the criteria in the preceding sentence and do not require reporting to the IRB. They should be reported to the sponsor as described in the protocol and written documentation of their occurrence filed with the investigator's study records.

8.2 Reports and Recording

All PDs must be recorded in the research file and in OnCore per CTO SOP SCON13 Reporting Unapproved Protocol Deviations (Appendix 8). The investigator is required to submit all Major PDs that are unplanned and unintentional to the IRB within5 days. For interventional investigator initiated studies reviewed by the DSMC, the investigator is required to submit all Major PDs to the DSMC Medical Monitor, with a copy to the DSMC Chair or Vice Chair, within 24 hours of becoming aware of the event.All PDs will be reported to the DSMC as required by the risk level assigned to the study. However, if the Medical Monitor determines corrective action is necessary, an “ad hoc” DSMC meeting will be called. Sites of multi-site investigator initiated trials for which UICC is the lead site are required to enter all PDs into UICC’s Clinical Trials Management System, OnCore. In addition, clinical trial sites are required to submit Major PDs electronically to the DSMC according the same timeframes as for local MajorPDs. Reporting requirements for Phase III investigator-initiated studies are described in the DSMP reviewed by the PRC and UIC IRB.

9. Quality Assurance

9.1 Quality Assurance Unit

The Quality Assurance Unit (QAU) is administratively managed in the CTO and is charged with ensuring protocol compliance with all UICC policies and procedures, IRB policies, FDA regulations, ICH-GCP, CTMB guidelines, and CCSG guidelines, as well as adherence to the protocol through auditing and monitoring activities performed throughout the year. All studies approved by the PRC fall within the Unit’s purview regardless of study type and sponsor. While administratively located within the CTO, the auditor reports to the Associate Director for Clinical Research and the DSMC.

The QAU is directly responsible for conducting audits of all UICC NCTN prospective registries and therapeutic studies, as well as required and ad hoc DSMC audits as described in CTO SOP SCON18-1 Internal Monitoring & Auditing (Appendix 9). Audits include the review of consent, eligibility, treatment, AEs/SAEs, adherence to study parameters, accuracy of case report forms, drug accountability, and review of the regulatory file. The QAU oversees the creation of any corrective and preventative action plans (CAPAs) to ensure that issues are addressed satisfactorily and the QAU will then follow-up and confirm the staff’s compliance with the CAPAs.

For externally monitored studies, the QAU receives all study monitor reports. The QAU identifies issues and trends emanating from those reports. The QAU also participates in external audits of studies performed at UICC as described in CTO SOP SCON18-2 External Auditing (Appendix 10). The results of audits and reporting of trends are presented to the Clinical Research Executive Committee and, for investigator initiated

clinical trials, to the DSMC. Major concerns about PI behavior, scientific misconduct, or systemic issues are reported to the Associate Director for Clinical Research.

9.2 Quality Assurance Auditing

The frequency of auditing and percentage of cases audited is determined by the type of study being audited. All investigator initiated clinical trials are audited quarterly and all other studies eligible for audit are reviewed every 6 months.

9.2.1 Auditing Standards

The audit will be conducted in accordance with internal policies and the NCI Clinical Trials Monitoring Branch audit guidelines to ensure the accuracy of data, adherence to the protocol and the protection of human subjects.

9.2.2 Case Selection

Once a clinical trial is identified for auditing, the QAU staff member or designee arranges for a random selection of cases to audit from among all subjects registered in the database, as specified in section 4.6. If subjects of UIC affiliate sites are enrolled, cases from those sites are randomly selected for review as well. Copies of these case materials are to be sent by the affiliate to UIC for review.

9.2.3 Study Team Notification

The Principal Investigator and Study Coordinators are notified in advance of the audit. The QAU staff contacts the study team to arrange for a mutually agreed upon time for the auditing session.

9.2.4 Audit Preparation

The investigator and the research staff are responsible for gathering all of the materials germane to the review, including Medical records, case reports forms, and any other research records as requested. If affiliate sites are enrolling subjects, materials needed for the review from the outside centers must be provided to the Quality Assurance Specialist.

9.2.5 Audit Focus

Audits have three primary areas of focus:

1. Regulatory/IRB procedure compliance: Review of current protocol, amendments, participant consent form, adverse event submissions, and continuing review documents.

2. Pharmacy/IND procedure compliance: Review of procedures for drug storage, a system for tracking IND drugs and drug accountability.
3. Case records: Each case audited is reviewed to determine that there is a signed and dated participant consent form, the subject has met the eligibility criteria, received the correct treatment, dose modifications per protocol (if required), that there is an objective treatment response, and any toxicities are documented and reported to the UIC IRB.

9.2.6 Access to Information

The UICC investigator is required to provide the audit staff with access to all source documentation. Source documentation may include, but is not limited to the following:

1. Inpatient and outpatient Medical records, including progress notes, diagnostic reports (imaging studies, ECGs, pathology reports), laboratory data, and admission forms
2. Study flow sheets and other research records that are signed and dated
3. Appointment books
4. Subject diaries/calendars

9.2.7 Exit Interview

At the end of each audit visit, an exit interview with the auditor, PI, and study staff takes place. During this time, all audit findings are reviewed and discussed, and any questions can be answered. Additionally, the PI and study staff will receive a copy of the audit report, which includes corrective action items.

9.2.8 Distribution and Review of Audit Reports

Investigator initiated clinical trial audit reports are submitted to the DSMC for a review of the findings and follow up actions as appropriate and all audit reports are sent to the PI, study team, and findings distributed to the staff managers as necessary. A copy of the report and recommended DSMCactions, if applicable, is sent by the PI to the IRB via an IRB prompt report. The committee regards the review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The DSMC may, based on the audit report, request modifications to, suspend or terminate the trial.

9.2.9 DSMC Action Based on Audit Report

Audit reports for investigator initiated clinical trials are presented at the next scheduled DSMC meeting. The DSMC can take the following actions:

1. Accept the report without further comment.

2. Accept the report with recommended/required changes to the protocol and/or participant consent form as evidence by the submission of amendments to the protocol and/or participant consent form as required.

3. Recommend the suspension of the study accrual until the necessary amendments have been submitted and approved by the PRC and IRB as required.

4. Ask the investigator(s) and/or research staff for additional information pending action

5. Suspend accrual to study

A copy of the final audit report, including the DSMC's determination and recommendation, as relevant, is provided to the UICC investigator with instructions to submit the report to the UIC IRB. If the DSMC determines that a study should be closed or suspended (pending submission of amendments to the protocol and/or participant consent form), the DSMC notifies the PRC and UIC IRB.

9.3 Additional Randomly Selected Audits

In addition to the risk-level dependent audit frequency, the QAU may elect to perform random audits of participants entered into interventional UICC trials to verify that there is a signed and dated patient consent form, that the participant has met the eligibility criteria, and that AEs/SAEs are documented and reported to the sponsor if applicable and the UIC IRB.

9.4 For Cause Audits

Any study of UICC may also be audited at any time by the QAU at the request of the DSMC, PRC, IRB, and/or the UICC Associate Director of Clinical Research. Reasons for special audits may include prior monitoring or audit findings, allegations of scientific misconduct, and where significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

9.5 UICC Investigator-Initiated Multi-Site Trials

The PI is ultimately responsible for monitoring compliance at all participating sites and has the authority to suspend and/or close a participating site based on lack of compliance.

Institutions participating in UICC lead investigator-initiated interventional multi-center trials may self-monitor. They are required to follow the UICC DSMP and CTO Internal Audit SOP or, if an NCI Designated Cancer Center, they may follow their own NCI approved Data and Safety Monitoring Plan. Alternatively, an external monitoring entity can be used to monitor the trial if the UICC DSMP and CTO internal audit SOP are followed. The site must forward a copy of the final audit report to the PI and study staff.

The audit report is submitted by the UIC PI or study staff to the DSMC for review and action. A copy of this report and recommended DSMC action is sent to the PRC and IRB. The UIC IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

In addition, participating institutional investigators must, on an ongoing basis, submit case report forms with copies of corresponding source documentation (as described above) to the principal investigator for each participant entered into the study. The principal investigator or his/her designee is responsible for reviewing documentation submitted by the participating institution for accuracy.

Each participating institutional investigator is required to submit all serious on-site adverse events to the UICC principal investigator within 1 business day of awareness of the event. The UICC principal investigator must submit information regarding non local SAEs to the DSMC, and to the UIC IRB consistent with the requirements for the submission of non-local adverse events, and other regulatory agencies as necessary (e.g. FDA for IND trials).

Any SAEs occurring at UIC must also be reported to participating sites in accordance with the same timeframes as listed above for sites reporting to UIC. The participating sites will be responsible for reporting UIC SAEs to their respective IRB in accordance with their institutional expedited reporting policies.

Appendix 1: Abbreviations

CTO	Clinical Trials Office
CRC	Clinical Research Coordinator
CTAC	Clinical Trials Advisory Committee
CTEP	Cancer Therapy Evaluation Program
DM	Data Manager
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
EDDO	Early Drug Development Office
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IND	Investigational New Drug
IRB	Institutional Review Board
MM	Medical Monitor
NCI	National Cancer Institute
NIH	National Institutes of Health
CTO	UICC Clinical Trials Office
OHRP	Office for Human Research Protections
PHI	Personal Health Information
PI	Principal Investigator
PRC	Protocol Review Committee
PSU	Protocol Support Unit
QAU	Quality Assurance Unit
SAE	Serious Adverse Events
UICC	University of Illinois Cancer Center
UIC	University of Illinois, Chicago

Appendix 2: DSMC Summary ReportProtocol SAE Counts

Protocol No.:		Library:		PI:				Sponsor:
Protocol Target Accrual:			Accrual To Date:					Protocol Status:
CC Total Accrual Goal (Upper):								IRB Expiration:
Short Title:								
Sources:								
Protocol SAE Counts								
Arm	**Category**	**Adverse Event Detail**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
Relapse or Progression Total								

Subject Specific Events Details

Study Site	Subject MRN	Subject Name	Event No.	Event Date	Follow-Up No.	Hospitalization	Death Occurred (days)	Adverse Event Details		
								AE Detail	**Grade**	**Attribution**

Subject Deviations Details

Study Site	Subject MRN	Subject Name	Deviation Category	Deviation Description	Date Discovered	Deviation Date	Effect on Patient Safety	Action Taken	Role Responsible for Action Taken	Has the integrity or validity of the data been compromised?	Was an IRB waiver granted?	IRB Reported Date

Protocol Toxicity Summary (AE Details are color coded to highlight trends)

Study Site	Subject MRN	Subject Name	Event No.	Event Date	Follow-Up No.	Hospitalization	Death Occurred (days)	Adverse Event Details		
								AE Detail	**Grade**	**Attribution**

Protocol SAE Report

Protocol No	PI	Protocol Status	SAE #	Overall Protocol Attribution	AE Grade	Event Narrative	AE Category	AE Detail	AE DLT	Source	Source Attribution	Event Date	Event End Date	Reported Date	Death Date	Death Occurred

Custom SAE Data Report

Protocol Details	Protocol Accrual	Protocol Disposition	Protocol Demographics	Protocol Status History	Protocol Responses	Protocol Survival	Protocol Accrual History	Subject Deviations	Protocol SAEs

Appendix 3: Medical Monitor Report Template
Data Safety Monitoring Committee (DSMC)
Medical Monitor/ Biostatiscian Report

IRB #:	
Principal Investigator:	
Protocol Title:	
Study Risk Level	☐ Low ☐ Medium ☐ High

Status of protocol:
☐ Open, accruing ☐ Suspended ☐ Open, not-accruing ☐ Closed ☐ Hold

Study Type: ☐ Single Institution ☐ Multi-Institutional

Review Type:
☐ SAE (complete section A within 48 hours of receipt)
☐ Protocol Deviation (complete section B within 24 hours of receipt if serious, unexpected and related, 48 hours for all others)
☐ Dose Escalation/Cohort Expansion (complete section C by 48 hours prior to the DSMC meeting)
☐ Routine Review (complete section D by 48 hours prior to the DSMC meeting)

Review Instructions: Complete the section corresponding to each review type indicated AND section E, Preliminary Study Outcome Recommendation.

A. SAE:
Do you agree with how the SAE was categorized/attributed by the study team?: ☐ Yes ☐ No
If no, indicate areas of disagreement:

Do you recommend any changes to the SAE attributions?: ☐ Yes ☐ No
If yes, please specify and provide a rationale for this change:

Is corrective action necessary to alleviate risks to subjects (requires an Ad Hoc DSMC meeting)?:
☐ Yes ☐ No
If yes, please specify suggested corrective action:

Do you recommend any changes to the study protocol?: ☐ Yes ☐ No
If yes, please specify:

Do you recommend study closure?: ☐ Yes ☐ No
If yes, please justify reasons for study closure:

Was this SAE a Dose Limiting Toxicity?: ☐ Yes ☐ No
If yes, please complete section C below.

B. Protocol Deviation:
☐ Major Protocol Deviation ☐ Minor Protocol Deviation

Is corrective action necessary to alleviate risks to subjects (requires an Ad Hoc DSMC meeting)?:
☐ Yes ☐ No
If yes, please specify suggested corrective action:

Do you recommend any changes to the study protocol?: ☐ Yes ☐ No
If yes, please specify:

Do you recommend study closure?: ☐ Yes ☐ No
If yes, please justify reasons for study closure:

C. Dose Escalation/Cohort Expansion:
Total Number of DLTs:

Number of DLTs per each dose level:

Do you approve escalation to the next cohort, if applicable: ☐ Yes ☐ No

Do you recommend any changes to the study protocol?: ☐ Yes ☐ No
If yes, please specify:

Do you recommend study closure?: ☐ Yes ☐ No
If yes, please justify reasons for study closure:

D. Routine Review:

Are there any issues regarding accrual trend or history? ☐ Yes ☐ No
If yes, please specify:

Are there any issues regarding SAE trend or history? ☐ Yes ☐ No
If yes, please specify:

Are there any other issues and/or study flaws that need to addressed? ☐ Yes ☐ No
If yes, please specify:

E. Preliminary Study Outcome Recommendation (Required for all reviews, check all that apply):
☐ **Full Approval**
☐ **Conditional Approval**
Specify approval conditions:

☐ **Suspension**
Specify conditions for lifting suspension:

☐ **Closure**
☐ **Recommended protocol amendments**
Specify recommended amendments:

☐ **Other corrective actions (please specify):**

Medical Monitor/Biostatistician Signature: _____

☐ **Primary Reviewer**
☐ **Secondary Reviewer**

For DSMC Administration Use Only

Final Committee Decision (check all that apply):
☐ **Full Approval**
☐ **Conditional Approval**
Specify approval conditions:

☐ **Suspension**
Specify conditions for lifting suspension:

☐ **Closure**
☐ **Recommended protocol amendments**
Specify recommended amendments:

☐ **Other corrective actions (please specify):**

Re- review study in:
☐ **3 months**
☐ **6 months**
☐ **1 year**
☐ **Other:**

<u>If applicable</u>:

DSMC Meeting Date

Agenda #

Appendix 4: Protocol Review Committee Roster

Michael Berbaum, PhD	Director- Methodology Research Core, Adjunct Associate Professor, Director- Biostatistics Core	Institute for Health Research and Policy, Division of Epidemiology and Biostatistics, Center for Clinical and Translational Science
Noah Birch, MD, PhD	Assistant Professor	Hematology/Oncology, Department of Medicine
Yolande Chen, MD	Assistant Professor	Hematology/Oncology, Department of Medicine
Zhengjia Nelson Chen, PhD	Associate Professor, Director of Biostatistics Core, Shared Resources	University of Illinois (UI) Cancer Center, School of Public Health Epidemiology an Biostatics
Ahmad Daher, MD, PhD, *Chair*	Assistant Professor	Department of Neurology and Rehabilitation Medicine
Cristiana Hentea, MD	Assistant Professor	Department of Pediatrics
Abiola Ibraheem, MD	Assistant Professor of Clinical Medicine	Hematology/Oncology, Department of Medicine
Linda Kaste, PhD, DDS, MS	Professor	Department of Oral Biology
Mark Korpics, MD	Assistant Professor	Department of Radiation and Cellular Oncology
Nadim Mahmud, MD, PhD, *Vice Chair*	Professor, Director of Clinical Stem Cell Laboratory	Hematology/Oncology, Department of Medicine
Joel Schwartz, DMD, DMedSc	Professor & Director of Oral Pathology Biopsy Service	Oral Medicine and Diagnostic Sciences
Desmona Strahan, MS	Research Specialist	Committee Community Engagement Member, Community Engagement Health Equity (CEHE)
Karen Sweiss, PharmD, BCOP	Assistant Professor	Department of Pharmacy Practice
Debra Tonetti, PhD	Professor	Department of Pharmaceutical Sciences
Lisa Tussing-Humphreys, PhD, MS, RD	Associate Professor, Director of Diet and Behavior Shared Resource (DBSR)	Kinesiology and Nutrition, UI Cancer Center
Michael Warso, MD	Professor of Surgery	Division of Surgical Oncology, Department of Surgery
Frank Weinberg, MD, PhD	Assistant Professor of Clinical Medicine	Hematology/Oncology, Department of Medicine
Gina Menyah	N/A	Committee Patient Advocate Member

Appendix 5: DSMC Membership Roster

Sandra Cuellar-Puri, Pharm. D., BCOP	Associate Professor	Department of Pharmacy Practice, Ambulatory Pharmacy Service
Kent Hoskins MD, BA	Professor	Hematology/Oncology, Department of Medicine
Shikha Jain, MD, FACP	Associate Professor	Hematology/Oncology, Department of Medicine
Li C. Liu, PhD	Associate Professor	Department of Epidemiology and Biostatistics
Stefania Maraka, MD	Assistant Professor	Department of Neurology and Rehabilitation Medicines
Damiano Rondelli, MD, *Chair*	Professor	Hematology/Oncology, Department of Medicine
Paul Rubinstein, MD, *Vice Chair*	Associate Professor	Hematology/Oncology, Department of Medicine
Mary Lou Schmidt, MD	Professor	Hematology/Oncology, Department of Medicine
Santosh Saraf, MD	Associate Professor	Hematology/Oncology, Department of Medicine
Jiehuan Sun, PhD	Assistant Professor	Department of Epidemiology and Biostatistics
Karen Xie, DO	Associate Professor	Department of Radiology

Appendix 6: Protocol Review and Monitoring System
Protocol Review Committee (PRC) Policies & Procedures

UI Health | UIC
UNIVERSITY OF ILLINOIS CANCER CENTER
PROTOCOL REVIEW COMMITTEE

Protocol Review and Monitoring System
Protocol Review Committee (PRC) Policies & Procedures

Policy Update:

This document outlines the Protocol Review and Monitoring System (PRMS) responsibilities of the University of Illinois Cancer Center. These responsibilities are primarily carried out by UI Cancer Center Protocol Review Committee (PRC). A summary of the changes is included here. All forms are found attached at the end of the document.

Version:	2.3
Last Reviewed:	4/29/2024
Effective Date:	

Cancer Center Approval

Title: Cancer Center Deputy Director

Approval Signature: **Date:**

_____ _____

Protocol Review and Monitoring System (PRMS)
Protocol Review Committee (PRC) Policies & Procedures

Revision History

Version #	Date	Section	Details of Changes
2.3	04/25/2024	Introduction, New Study Submissions, New Study Review Outcomes, and PRC Membership and Meeting Organization	Added the NCI definition of Clinical Research; Added detail that the disease team minutes should have clear documentation regarding protocol prioritization; Added detail for studies who receive Modifications Required or Disapproved decisions; The PRC Chairs report to the Cancer Center Deputy Director
2.2	02/22/2024	Levels of Review (Expedited Review) and Protocol Prioritization	Added detail on other types of expedited reviews; Changed who is responsible for protocol prioritization
2.1	01/30/2024	PRC Membership and Meeting Organization and New Study Submissions (Exempt)	Addition of the process of how PRC committee members are trained; Clarification that single patient INDs are exempt
2.0	07/18/2023	New Study Submissions (Expedited Review) and Protocol Amendments	Removal of the exclusion of Expanded Access Protocols from PRC review and clarification that an amendment is to be submitted with the addition or deletion of study sites
1.9	11/15/2021	PRC Membership and Meeting Organization	Addition of a community engagement member to the committee
1.9	11/15/2021	Forms	Updating the Patient Advocate Form to also be the Community Engagement Member form
1.9	11/15/2021	New Study Submissions	Addition of Data Safety Monitoring form and protocol summary form as required submission documents for interventional studies.
1.8	07/01/2021	New Study Review Outcomes	The review outcome Disapproval now states that there is a 30 day timeframe for a re-review.
1.8	07/01/2021	PRC Membership and Meeting Organization	Addition of a Patient Advocate to the committee.
1.8	07/01/2021	Forms	Addition of a patient advocate reviewer form and minor revisions to initial reviewer form.

Protocol Review and Monitoring System (PRMS)
Protocol Review Committee (PRC) Policies & Procedures

1 Definitions

CCSG	Cancer Center Support Grant
CRLC	Clinical Research Leadership Committee
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
EAP	Expanded Access Protocol
IRB	Institutional Review Board
NCI	National Cancer Institute
PI	Principal Investigator
PRC	Protocol Review Committee
PRMS	Protocol Review and Monitoring System
UI Cancer Center	University of Illinois Cancer Center

2 Introduction

The PRMS responsibilities required for the CCSG are primarily carried out by the UI Cancer Center's PRC. The purpose of this policy is to document the review processes undertaken by the PRC.

The PRC (also known as a Scientific Review Committee) evaluates all clinical research studies undertaken by the UI Cancer Center and its affiliates and conducted by UIC faculty, involving patients with cancer or individuals at risk for cancer. The NCI defines clinical research as one of three categories below:

- Patient-oriented research: This type of research is conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual, tissue banking, and studies that do not require patient consent (e.g., retrospective chart reviews). Patient-oriented research includes:
    - Studies of mechanisms of human disease
    - Studies of therapies or interventions for disease
    - Clinical trials, and
    - Studies to develop new technology related to disease
- Epidemiological and behavioral studies: Studies among cancer patients and healthy populations that involve no intervention or alteration in the status of the participants, e.g. surveillance, risk assessment, outcome, environmental, and behavioral studies.
- Health services research: Protocol designed to evaluate the delivery, processes, management, organization, or financing of health care.

The Protocol Review Committee is responsible for:

- Undertaking scientific review of all new studies
- Assessing general feasibility, annual accrual expectations, and competing studies
- Assigning risk according to the UI Cancer Center's DSMP and informing the UI Cancer Center DSMC
- Reviewing all protocol amendments that affect study design
- Maintaining written records of all meetings
- Monitoring accrual and ongoing scientific relevance for all studies
- Requesting corrective action plans for poorly accruing studies and closing studies that do not meet accrual expectations

3 Procedures

3.1 New Studies

All research studies requiring PRC review must be submitted to PRC and approved prior to submission to the IRB. All new study applications are reviewed by PRC administrative personnel to determine what level of review is appropriate. Studies may receive full committee, expedited review, administrative review, or be deemed exempt from PRC review.

New Study Submissions

For new studies, the PI or Submitter creates a new study record via the ePRMS submission console using the OnCore Clinical Trials Management System (CTMS). In addition, the following documents must be uploaded to the record.

- Final Protocol
- Prospective hypothesis driven studies: Disease Team Minutes for the meeting where the study was approved when required (see UI Cancer Center Disease Team Policy)
    - Disease Team Minutes should include clear documentation justifying the reason for opening the study in the event of any study portfolio conflicts with other studies enrolling the same population of the study being submitted
- PI NIH Biosketch, if NIH Biosketch is not available a curriculum vitae (CV) may be substituted
- Protocol Supporting Documentation, this includes but is not restricted to: Scientific Approval Letter from designated site, Surveys, Questionnaires, etc.

Additional requirements for interventional studies only:

- UICC PRC Data & Safety Monitoring Plan (DSMP) Form: A study specific DSMP is required if the study is an Interventional clinical trial. If the study is a phase III investigator initiated therapeutic clinical trial, the DSMP needs to include plans for an independent Data and Safety Monitoring Board (DSMB).
- Protocol Summary Form

Levels of Reviews

There are four levels of PRC review:

- Exempt

- Administrative
- Expedited
- Full Committee

Exempt from PRC Review

The following types of studies are exempt from PRC review.

- Retrospective chart review studies
- Institutional registries, databases, and serum and tissue banking protocols where there are no research hypotheses
- Single patient INDs

Exempt studies are not required to be entered into OnCore. If the study qualifies under the exempt criteria, email the protocol to the PRC administrative personnel for an exemption letter. If approved, the PRC administrative personnel will provide an exemption letter that must be included in the Initial IRB submission.

Administrative Review typically includes:

1. NCI-approved cooperative group studies (National Clinical Trials Network) and NCI Cancer Therapy Evaluation Program (CTEP)-approved studies.

2. Multi-site institutional trials previously approved by a PRMS from another NCI-designated Cancer Center. Documentation of the external PRC approval must be on file with the UICC PRC.

3. Prospective, hypothesis-driven, non-interventional studies (e.g., observational, ancillary, or correlative studies) that are not investigator initiated.

For studies meeting the administrative review criteria listed above, the PRC administrative personnel will review all submission materials and assure that the criteria above is met. If no substantive issues are identified during the administrative review, PRC administrative personnel will then generate an approval letter that is emailed to the PI. Administrative reviews are typically communicated within 3 business days of receipt. A summary report of all studies that received administrative review since the last PRC Full Committee is included in the agenda and noted in the minutes.

Expedited Review typically includes:

1. Investigator-initiated studies that have or will receive external peer-review and funding by an approved NIH peer-review funding organization prior to activation. Extramurally funded studies that do not include a protocol as part of the peer-review process may, at the PRC Chair's discretion, undergo a Full Committee Review.

2. Prospective, hypothesis-driven, non-interventional studies (e.g., observational, ancillary, or correlative studies) that are investigator initiated.

3. Expanded Access Protocols (EAPs), that is industry-initiated protocols where the primary objective is to provide rapid access to an unapproved drug to patients [See also industry-initiated studies in Full Committee Review below]

4. Annual Continuation Reviews (see section 3.2) and replies to Response to Modification Required determinations (see section 3.1).

For studies that meet the expedited review criteria listed above, the PRC Chair will review all submission materials and perform an expedited review, assuring that conflicts with current studies do not exist, resources appear appropriate to implement and complete the study, and that appropriate data and safety monitoring and recruitment plans are in place. If no substantive issues are identified during the Chair's review, PRC administrative personnel will then generate an approval letter that is emailed to the PI. In the event that a conflict of interest exists and/or the Chair is an investigator on the study being reviewed, the Vice Chair will conduct the review. Expedited reviews are typically communicated within ten business days of receipt. A summary report of all studies that received expedited review since the last PRC Full Committee is included in the agenda and noted in the minutes.

Note that any of the above types of studies may, at the PRC Chair's (or Vice Chair's) discretion, be required to undergo a Full Committee Review.

Full Committee Review

Studies that do not meet criteria for administrative or expedited review or exemption will receive full committee review.

Studies eligible for full committee review typically include the following:

1. Interventional Investigator-initiated studies: These generally are studies developed by UI Cancer Center faculty with funding from the institution, a non–peer-reviewing agency, or industry. Multi-institutional investigator-initiated studies where the study PI is at another non–NCI-designated institution and the study has not undergone formal peer review (as outlined in the Expedited Review criteria above) also require full committee review.
2. Industry-initiated studies: The concept and protocol for these studies are developed by a company. There is an exception to this requirement for EAPs, since their primary objective is to provide rapid access to an unapproved drug to patients (see above).

Full committee review focuses on the scientific merit of the study, prioritization of the study within the larger portfolio, competing studies, and accrual feasibility. Committee members will address all scientific aspects of a proposed study according to defined review criteria, including but not limited to:

- The study addresses a relevant scientific question
- The primary and secondary objectives are scientifically sound

- The study design is appropriate to meet the objectives
- The response criteria and endpoints are clearly defined
- The sample size is appropriate to answer the question, accrual goals are clearly stated and the patient population is sufficient to meet accrual goals
- The data and safety monitoring plan is appropriate
- The early stopping rules are adequate and clearly described
- The investigator has an appropriate plan for the inclusion of women and minorities

Reviewers will also assign a level of risk to Investigator Initiated studies which will determine the recommended level of auditing and monitoring of the DSMC.

PRC Submissions for NIH JIT Requests and IRB Submissions for Core/Center Grants.

If a submission to the IRB is in response to an NIH Just In Time (JIT) request, then all documents and processes for both PRC and IRB review are required.

If the submission is for a Core/Center grant, a Training grant, a grant where human subject involvement will depend on the development or completion of instruments, procedures, or prior non-human studies, as defined by the IRB, or is for a grant submission that has not yet been approved for funding by a peer reviewing funding agency (grant is pending review) but the investigator needs to seek IRB approval, then the PRC will not review the application. However a letter will be issued to the PI stating that the submission is granted an approval by the PRC *contingent* upon funding by the granting agency and approval by the IRB. However, prior to the involvement of human subjects, the use of identifiable subject information, and/or pilot testing of instruments or procedures, a protocol describing the human subjects activities must be reviewed and approved through the appropriate review process described above.

Process for Protocols Included in Grant Submissions to Extramural, Peer Reviewing Agencies

If a grant submission has already been reviewed and approved for funding by a peer reviewing funding agency, an expedited approval letter from the committee will be issued to the PI provided the study has all of the required protocol elements

Click this link to view organizations with Peer Review Funding Systems

Protocol Prioritization

NCI guidelines require that a mechanism be established within a cancer center for prioritizing competing research studies that may enroll subjects with similar eligibility criteria. At the UI Cancer Center studies are prioritized by PRC administrative staff upon submission and confirmed by the PRC reviewer. The PRC prioritizes studies utilizing the scoring scale below, with 1 representing the highest priority, and which mirrors the priorities of the UICC. This score is captured in the OnCore CTMS. The scoring system is based on protocol type, sponsorship, and potential for scientific impact. The PRC utilizes this score to prioritize studies on meeting agendas.

Table 1. Protocol Prioritization Scoring Scale

Study Originator	Study Type	Score
IIT	Treatment	1
NCTN	Treatment	2
Foundation or External IIT	Treatment	3
Industry	Treatment	4
IIT	Interventional	5
NCTN	Interventional	6
Foundation or External IIT	Interventional	7
Industry	Interventional	8
IIT	Non-interventional	9
NCTN	Non-interventional	10
Foundation or External IIT	Non-interventional	11
Industry	Non-interventional	12

Determination of Risk

Each UI Cancer Center study undergoes scientific review by the PRC, in part to ensure that procedures are in place to ensure the safety of subjects depending on the degree of risk of the study. The PRC assigns a category of risk to every UI Cancer Center investigator initiated clinical trial and the DSMC follows the plan of review for that category.

The purpose of assigning a level of risk (low, moderate, or high) is to ensure that data and safety monitoring activities are appropriate for the level of subject risk. In order to make a decision, the PRC reviews the following criteria:

- Expected duration of the study based on the study design and estimated rate of enrollment.
- Study population (e.g. children, pregnant women).
- Procedures to ensure the safety of subjects in accordance with the degree of risk.
- Methods to ensure the validity and integrity of the data, including adequate biostatistical design and appropriate data analysis.
- Adequate data management systems including case report form records and a plan for data collection.
- Procedures for reporting serious adverse events to the appropriate departments/committees (e.g. IRB, FDA, NIH).
- The number of sites involved in the clinical trial.
- The specific risks known to be associated with a particular treatment/intervention

The risk level determines the frequency of monitoring for a protocol, which may be altered (i.e., increased) as and if issues arise.

Definition of Risk Levels

There are three levels of risk that may be assigned: High, Moderate and Low. Each category is described below. Please reference the UI Cancer Center's DSMP for monitoring frequency based on risk assignment.

High Risk

Studies assigned to the high-risk category include any therapeutic investigator-initiated pilot, phase I, II, or trials involving IND/IDEs, investigator-initiated multi-center trials, as well as any research involving recombinant DNA molecules (gene transfer) and cell-based therapies. These clinical trials will be reviewed on a quarterly basis by the DSMC.

Moderate Risk

Studies assigned to the moderate-risk category include most investigator-initiated, single center, Phase I or II trials using FDA-approved, commercially available compounds. Moderate Risk trials will be reviewed biannually (every 6 months) by the DMSC.

Low Risk

Studies assigned to the low-risk category include investigator initiated non-therapeutic trials. Low risk trials will be reviewed annually by the DSMC.

Protocol Review and Response Expectations

Study submissions that have been received 13 BUSINESS days prior to the scheduled PRC meeting will be assigned to a minimum of 3 reviewers by the PRC Chair. Studies submitted after 13 business days will be assigned to the next scheduled PRC meeting.

- For treatment studies two reviewers **must be** treating physicians, and the third reviewer must be a statistician. Additional reviewers may be assigned as appropriate.
- For non-treatment studies, two researchers with relevant expertise may be assigned as reviewers, and the third reviewer must be a statistician.

Reviewers are required to complete PRC review forms (accessed in OnCore) prior to the PRC meeting in order for the protocol to be discussed and voted on at the meeting. If review forms are not completed prior to the meeting, the protocol may be tabled until the next PRC meeting, at the Chair's discretion.

The PRC review outcome will be emailed to the PI and the Submitter no later than ten business days following a meeting with an electronic copy of a signed letter containing a summary of the committee's deliberation and comments if applicable. Please note that after receiving the PRC decision letter the PI should provide a response within 15 business days for a "modifications required" outcome. If no response is received, the study will be disapproved at the discretion of the PRC Chair.

New Study Review Outcomes

Once the new study review is completed, the PRC administrative personnel will prepare a review outcome notification that will be issued to the PI and Submitter. Review outcomes include the following:

- Approved
  - The study is approved for activation as submitted and may proceed to the IRB. The PI and Submitter will receive an approval letter.
- Modification Required
  - The study review results in concerns that require a PI response which may include minor modifications to the study or study materials. PI and Submitter will receive a letter requesting a written response to the committee's required changes and a tracked change version of the protocol, if protocol modification are made in response to required changes. Should the response be found to be satisfactory, as determined by the PRC Chair or the original reviewers, the PI and Submitter will receive a final approval letter. If the PI does not respond within 15 days of receiving PRC decision letter, the study will be disapproved at the discretion of the PRC Chair.
- Disapproved
  - The study does not satisfy the review criteria and significant revisions to the study are necessary. PI will receive a letter requesting a written response to the committee's required changes and a tracked change version of the protocol if protocol changes are made as part of the response. The study must be re-submitted and reviewed at a full committee meeting. If all concerns are addressed, the PI and Submitter will then receive a final approval letter.
  - If the PI does not respond to the PRC within 30 days of receiving such a PRC decision letter, the study may not be accepted, at the discretion of the PRC Chair.
  - Studies that are disapproved twice and subsequently resubmitted to the committee may not be accepted, at the discretion of the PRC Chair.

3.2 Annual Continuation Review and Accrual Monitoring

Annual Continuation Review

Evaluation of the scientific progress of studies and how they fit into overall progress in their specific area of research is important to ensure that the study is continuing to address an important scientific question.

Studies are reviewed annually from the date of PRC approval, however the PI and/or Submitter can request to reset the annual review date to one year post IRB approval.

The purpose of the annual continuation review is to:

1. Evaluate major developments that occurred in the scientific area that affect the specific objectives of the study
2. Determine if sufficient progress is being made, including accrual
3. Monitor changes in the study's priority

4. Summarize any interim analysis and any significant study outcomes (e.g. met DLT, met accrual on specific study arm)

Annual Continuation Review Submissions

For all annual continuation review submissions, PI or Submitter creates a continuation record via the ePRMS submission console using the OnCore CTMS.
Submission requirements:

- PRC Annual Continuation Review Form; please note all fields are required
- Current protocol

The annual continuation review submission must be submitted to PRC prior to the PRC expiration date each year until the study is permanently closed to accrual.

Annual Continuation Review Process

Annual continuation review submissions are reviewed by the PRC Chair and Vice Chair, except as described in administrative review below. PRC administrative personnel will review each annual continuation review submission for completion and once complete, forward it to the PRC Chair and Vice Chair for review via an expedited review process. The PRC Chair and Vice Chair have the prerogative to refer any annual continuation review submission for full committee review (for example if there have been substantial modifications to the original protocol (see Section 3.4)).

Accrual Monitoring is an integral part of the annual continuation review process and must follow the guidelines as outlined in section 3.3.

Annual continuation review submissions that qualify for administrative initial review are reviewed by the PRC administrative personnel. In addition, full committee or expedited studies that have had no changes during the course of the year will be administratively reviewed. The PRC administrative personnel will assure that all criteria are met and that the submission is complete. PRC administrative personnel have the prerogative to refer any annual continuation review submission for expedited review by the PRC Chair and Vice Chair.

Annual Continuation Review Outcomes

After review by the PRC Chair and Vice Chair, PRC administrative personnel will either prepare a review outcome notification (approved for continuation or disapproved for continuation), or prepare the submission for full committee review. Review outcome notifications are issued to the PI and Submitter.

When a PI closes or terminates a protocol, the status must be updated in OnCore and an electronic communication will be sent to PRC administrative personnel stating that the research is closed to accrual. A continuing review is no longer required when a study has been closed to accrual.

3.3 Accrual Monitoring

Accrual monitoring will be conducted for all active interventional studies semiannually. Prior to the accrual monitoring meeting, PRC administrative personnel will run a report identifying the status of all studies and their accrual. PRC administrative personnel will send out requests for justification of continuance to the PI of studies not meeting expected annual target goals (see below). The PI will be given 15 business days to respond. The PRC Chair will then review PI responses at the PRC meeting and determine if the study will remain open.

Target Accrual Reporting

At the time of initial PRC submission, the investigator is required to project the estimated total accrual and the estimated total duration of the study accrual. These projections will be utilized by the PRC for monitoring accrual progress.

Every 6 months, PRC administrative personnel generates a report identifying prospective interventional oncology studies that are actively enrolling cancer patients/subjects with the following fields:

- Protocol Number
- PI name
- Study title
- Indication if the study targets a rare cancer
- Date the study was opened to accrual
- Any temporary suspensions and date when trial was re-opened
- Gender distribution
- Race distribution
- Ethnicity distribution
- Research Center's (RC) anticipated (lower) target accrual
- RC anticipated duration for accrual
- RC total actual annual accrual to date
- Percent Accrued = $\frac{\text{RC total actual annual accrual}}{\text{RC Annual Accrual Goal}} \times 100$

For those studies where the *Percent Accrued to Date* falls below 50% of the projected annual accrual, PRC administrative personnel will issue a written notification requesting a response or justification from the PI. The PI shall be given 15 business days to respond to the notice with a specific plan to increase accrual. The PI's response will be reported to the PRC Chair approximately one month following the report's generation. The PRC Chair will determine if the PI's response is acceptable and whether the study may continue as planned, requires further justification or additional information, or will be closed to accrual. During the review period, PRC administrative personnel will also monitor those studies that have attained or exceeded their accrual goals. PRC administrative personnel will send a notice of acknowledgment to the PI that accrual monitoring has occurred and accrual goals have been met. For studies that have exceeded their goals, the PI will be advised to consider whether a modification request to

applicable study sponsors and the IRB is warranted to increase accrual goals. The annual accrual goal may undergo a one-time change with justification to the PRC at the time of accrual monitoring.

Table 2. Summary of PRC Accrual Expectations and Action Guidelines

Study Accrual Status	Type of PRC Accrual Monitoring Review	PRC Actions
All Prospective Interventional Studies Involving Rare Cancers[1]	Annually	Approved for continuation if scientific aims remain relevant. Justification of continuation of studies with ≤1 accrual per year is required.
All Pediatric Prospective Interventional studies	Annually	Approved for continuation if scientific aims remain relevant. Justification of continuation of studies with ≤1 accrual is required. Pediatric studies with zero accrual or less than 50% will be exempt for maximum of 3 years. At the 2 year mark, a justification for continuance will be requested. At the 3 year mark the study will receive final warning for closure.
Interventional Studies opened < six months	Exempt	N/A
Interventional Studies opened > six months	*All Studies with the following accrual status are subject to PRC Accrual Review.* *See categories below for expected PRC actions*	
Percent Accrued to Date > 50%	Semiannually	Approved for continuation

[1] Please reference National Institutes of Health site for a list of rare cancers: https://rarediseases.info.nih.gov/diseases/diseases-by-category/1/rare-cancers

Percent Accrued to Date < 50%	Semiannually	1st Review: Contingently Approved. The PI will be informed that accrual will be closely monitored during the next quarter and if sufficient progress is not made, the PI will need to provide more justification and/or a revised corrective action plan. 2nd Review Should the PI either: - fail to provide a corrective action plan, *and/or* - fail to improve accrual, *and/or* - fail to demonstrate adequate screening activity then the PRC will require the PI to close the study. Should the PI: - Provide a corrective action response and/or demonstrate an improvement in the accrual and/or screening activities the accrual review may be approved. Decision to close study: PI will be requested to provide study closure documentation (communication with IRB and/or Sponsor).

3.4 Protocol Amendments

Protocol amendments for studies that have been reviewed by the PRC and affect the principal elements of the original protocol, including but not limited to: study rationale, response criteria, eligibility criteria, objectives, study design, addition or removal of study sites, treatment plan, sample size, stopping rules, or statistical plan, must be submitted to the PRC in concurrence with the IRB for review and approval. Amendments that do not impact the aforementioned areas do not require PRC approval.

Amendment Submissions

For all amendment submissions, PI or Submitter creates a change review record via the ePRMS submission console using the OnCore CTMS.
Submission requirements include:

- PRC Amendment Committee Amendment Review Form with summary and justification of changes
- Clean, revised protocol
- Track change version of protocol showing the changes in the amendment

Amendment Review Process

PRC administrative personnel will review each amendment submission for completion and once complete, assign it to the PRC Chair or Vice Chair for review, except as described in administrative review below. The PRC Chair and Vice Chair have the prerogative to defer any amendment for full committee review.

Amendment review submissions that qualify for initial administrative review are reviewed by the PRC administrative personnel. The PRC administrative personnel will assure that all criteria are met and that the submission is complete. If there is an addition or removal of a study site the PRC administrative personnel will confirm whether the risk level of the protocol has changed, and if so, notify the DSMC coordinator. PRC administrative personnel have prerogative to refer any amendment review submission for expedited review by the PRC Chair and Vice Chair.

Amendment Review Outcomes

After review by the PRC Chair or Vice Chair, PRC administrative personnel will either prepare a review outcome notification, or prepare the submission for full committee review, depending on the outcome. Review outcomes include, approval, modifications required or disapproval. A review outcome notification of “approval” is issued to the PI and Submitter. A review outcome notification of “modifications required” will include an explanation of which revisions were not acceptable and why, and may contain suggestions as to how the PI can make the revisions acceptable.

4.0 PRC Membership and Meeting Organization

The PRC meets biweekly. Cancellations or modifications may be allowed for holidays and other unforeseen circumstances and will be communicated Cancer center-wide. Meetings may be

recorded to assist with minutes and documentation. Meeting minutes are shared with the PRC Chair and Vice Chair, then are sent for approval to the Cancer Center Deputy Director.

Member Anonymity

The identity of the PRC members reviewing a particular trial will remain anonymous to the submitter of the protocol and to the general UI Cancer Center community, unless the reviewer requests to contact the submitting PI directly. If the submitting PI has questions or concerns about PRC comments, they are asked to submit these questions to the PRC administrative personnel who will reach out to the appropriate committee member for clarification. PRC administrative personnel will respond to the PI without revealing the identity of the reviewers.

Conflicts of Interest

A PRC member who is the PI of a study being reviewed at a PRC meeting must be recused from the meeting during the review, discussion, and voting on the protocol. A PRC member who is a Co-Investigator of a study being reviewed at a PRC meeting is allowed to be present for discussion, however he or she must abstain from voting. A PRC member that has a financial conflict of a study being reviewed at a PRC meeting must be recused from the meeting during the review, discussion and voting on the protocol.

PRC Membership

PRC membership will include broad representation across medical disciplines in order to provide the highest quality study reviews. The Cancer Center Director and the Cancer Center Deputy Director shall identify and appoint established researchers as PRC Chair and Vice Chair of the PRC, ideally two senior faculty representing different disciplines. Potential PRC members are identified by the Cancer Center Deputy Director and the PRC Chair and Vice Chair and presented for review and approval by the Cancer Center Director. PRC faculty members must be members of the Cancer Center. The following minimum experience criteria are expected: to be at least 3 years post-completion of fellowship, and have experience as PI through completion of at least 1 clinical study and publications on research study outcomes. The PRC faculty membership should be comprised of 60% senior faculty (full professor and associate professor). Junior faculty may be appointed, but must meet minimum experience criteria. The PRC voting membership also includes a biostatistician, a patient advocate, and a community engagement member.

PRC membership shall be a three year commitment with a two term maximum. Members are expected to attend 75% of meetings annually or membership may be revoked at the Chair's discretion.

Members of the PRC may not serve simultaneously on the IRB, the DSMC, or as Clinical Trials Office Medical Director, Associate Director of Clinical Research, or Cancer Center Deputy Director.

The PRC Administrator trains all new members on the review process, and provides them with a copy of the PRC Policy outlining their responsibilities. New members are then trained on how to conduct scientific reviews by the PRC Chair.

Initial and Ongoing Training Quorum

Meeting quorum is 50% of committee membership and must include the PRC Chair or Vice Chair and one biostatistician member.

Responsible Personnel

The Cancer Center Deputy Director, PRC Chair, Vice Chair and PRC administrative personnel are responsible for the execution of these policies and procedures. The PRC Chair and Vice Chair report directly to the Cancer Center Deputy Director.

PRC Appeal Process

PIs can appeal any PRC decision by submitting a written request for an additional review to the PRC. However, there is no appeal process beyond the PRC and the final PRC decision cannot be overturned. The protocol may be resubmitted at another time as a new protocol, provided there are substantial changes and/or modifications.

Appendix 7: SOP SCON12 AE-SAE Documentation & Reporting

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

University of Illinois Cancer Center | Clinical Trials Office			
Standard Operating Procedure			
STUDY CONDUCT (SCON) **SCON12 AE/SAE Documentation & Reporting**			
SOP Number:	SCON12	**Effective Date:**	08/28/18
Last Reviewed:	09/21/2020	**Policy Applies to:**	All Employees
Approval		**Responsibility**	
Cancer Center Approval Date: Title: CTO Administrative Director Approval Signature: _____		Responsibility for review and maintenance of this policy is assigned to: CTO Administrative Director Author and/or Designee: Darlene Kitterman, CTO Administrative Director	

POLICY OVERVIEW

This policy outlines the steps to follow for documenting and reporting adverse events (AEs) and serious adverse events (SAEs) at the University of Illinois Cancer Center and the Clinical Trials Office (CTO).

BACKGROUND

Subject safety is the highest priority during the conduct of a clinical trial. Investigators are required to report all adverse events (AEs) that occur during the active phase of a study and for a period of time after the study ends. It is the Principal Investigator's (PI) responsibility to routinely assess for patient safety and keep the sponsor, Institutional Review Board (IRB), and UICC Data and Safety Monitoring Committee (DSMC), if applicable, informed of any AEs or other issues affecting the risk/benefit ratio. The PI may delegate this task to another qualified individual involved in the trial, such as a Co-investigator, but may not delegate responsibility.

RESPONSIBLE PERSONNEL

A. Advanced Practice Nurse (APN) on the Pediatric Services team
B. Clinical Research Coordinator (CRC)

C. Co-investigator
D. Data Manager (DM)
E. Principal Investigator (PI)
F. Regulatory Coordinator (RC)

DEFINITIONS

A. **Adverse Event (AE)** – Any untoward or unfavorable medical occurrence in a human research study participant. An AE does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational agent. AEs encompass clinical, physical, and psychological problems. AEs most commonly occur in the context of biomedical research but can also occur in social and behavioral research.
B. **Serious Adverse Event (SAE)** – Any event that is life threatening, results in death, an inpatient hospitalization or prolongation of hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly/birth defect. Based on appropriate medical judgment, an event that may jeopardize the subject's health and require medical or surgical intervention to prevent one of the outcomes listed above is also an SAE. SAEs are not required to be related to the research.
C. **Unanticipated Problem (UP)** – Includes any incident, experience, or outcome that is unexpected ***and*** related or possibly related to participation in the research ***and*** suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

PROCEDURE

1. **Identification and Documentation**
    a. The PI, Co-investigator, APN/CRC, or other patient-facing staff assess the study subject at each visit or contact for AEs that may be present or have occurred since the previous visit. The APN/CRC will:
        i. Collect the details of the event and document completely in the medical record and/or research chart.
            1. AE Log – AEs are recorded on the subject specific AE log.
                a. Review the AE log and update the form as necessary.
                b. The investigator will review each entry, assess for severity and attribution, sign, and date the AE entry.
                c. ***Note***: All SAEs are also considered AEs and as such, should be included on the AE log.
            2. Use the protocol required criteria for the grading of AEs. The most common grading criteria in use is the Common Terminology Criteria for Adverse Events (CTCAE), current version 5.0 dated 11/27/2017.
        ii. Document the status of any ongoing, unresolved AEs.

iii. Document the details of any AEs that have resolved since the previous visit.
iv. Promptly request additional information/off site medical records as needed for reporting purposes.
v. An abnormal laboratory result(s) will not be considered an AE unless documented as clinically significant by a physician.

b. Consult the protocol for any specific guidelines for the management of AEs or SAEs.
   i. Subject safety is always the first priority.
   ii. Provide clinical care per protocol, if not contraindicated, to ensure subject safety.
   iii. In an emergency, the PI may consider consulting with the sponsor regarding the option of breaking the study blind, if applicable.

2. Reporting SAEs

a. The APN/CRC will promptly report all SAEs to the study sponsor as soon as possible after learning of the event. Consult the protocol and sponsor for specific requirements regarding events that require reporting, the method and timeliness of reporting.
b. After sponsor reporting, the APN/CRC will enter the SAE into OnCore within 2 business days and attach the sponsor report and supporting documentation, when applicable.
c. The RC will obtain the report from OnCore and determine if the event requires expedited reporting.
d. If RC determines it is reportable, the RC will email the CRC and request an emailed copy of the CTEP AERs report or other report.
e. If the event is determined to be reportable to the IRB of record, the RC will report the event to the IRB of record and document the submission in OnCore.
   i. After IRB acknowledgement is received, the RC will properly file all documentation.
f. If the study is a UIC investigator initiated clinical trial, the RC will report the SAE to the DSMC or, in the case of a phase III UIC investigator initiated clinical trial, to the DSMB, and as necessary to others as outlined in the study Data and Safety Monitoring Plan (DSMP).
g. If the study is a UIC investigator initiated clinical trial and the PI holds the IND or IDE for the investigational agent/device, report the SAE if it meets FDA requirements for reporting on an FDA form 3500A.
h. Report deaths due to all causes that occur within 30 days of the last dose of study medication to the sponsor, the IRB, and the DSMC/DSMB, if applicable, within the timeframes outlined in the protocol, IRB policy, the study DSMP, if applicable, and other regulatory agencies, if required.
   i. Consult the protocol, the study DSMP, if applicable, and regulations for specific timeline requirements.
   ii. Most studies require deaths to be reported as SAEs if they occur within 30 days of the last dose of study medication.
i. The DM will complete the Case Report Forms (CRFs) promptly with the information contained in the source documents, AE Log, and SAE form, following up with the APN/CRC or investigator regarding missing documentation.

3. **SAE Follow-Up**
    a. The APN/CRC and RC will work together to submit follow-up reports to the sponsor, IRB, DSMC/DSMB, and/or FDA, as applicable.
    b. Continue to follow the AE or SAE as outlined in the protocol, or more frequently if necessary.
        i. Document all follow-up in the medical record and/or research chart.
        ii. Report follow-up information to the sponsor, IRB, DSMC/DSMB, and/or FDA, as applicable, as it becomes available.
4. **Reporting Subject Injuries**
    a. If an AE results in additional costs to the patient, the APN/CRC will immediately inform the Financial Manager.
    b. If the study is externally sponsored, the Financial Manager will check the contact or award notice to determine if the sponsor is paying for subject injuries.
    c. If the sponsor is paying for subject injuries:
        i. The Financial Manager will instruct the APN/CRC to inform the sponsor of the injury.
        ii. The Financial Manager will determine the cost of the injury and provide the cost to the APN/CRC to inform the study sponsor.
            1. If the costs for the injury were generated at UIC, the Financial Manager will inform the Clinical Research Finance Office (CRFO) of the injury and will work with the CRFO to determine the cost of the injury and direct the charges to the study account.
            2. If the costs resulting from the injury were generated outside of UIC, the Financial Manager will request that the APN/CRC work with the patient to obtain bills and receipts for costs generated from the injury.
                a. If possible, the Finance Manager will have bills redirected to the UICC CTO for payment.
                b. The Finance Manager will arrange for payment of any bills resulting from the injury or will arrange for reimbursement of the patient for any costs resulting from the injury from the study account.
        iii. The Finance Manager will invoice the sponsor for costs for the injury.

REFERENCE(S) / RELATED POLICY(IES)

DHHS Common Terminology Criteria for Adverse Events (CTCAE), v5.0dated 11/27/2017
UIC Data and Safety Monitoring Plan

COLLABORATION

This policy was developed in collaboration with the following Departments:
University of Illinois Cancer Center, Clinical Trials Office (CTO)

ATTACHMENTS

A. Research Staff Roles and Responsibilities Related to Adverse Event Reporting
B. Adverse Event and Serious Adverse Event IRB Reporting Timelines

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

ATTACHMENT A

University of Illinois Cancer Center | Clinical Trials Office

Research Staff Roles and Responsibilities Related to Adverse Event Reporting

Roles	Responsibilities

PI	• Protect the safety of the subject
	• Determine if the event is an Adverse Event that rises to the level of a Serious Adverse Event
	• Document that he/she regularly reviews AE logs and SAE reports for accuracy by signing all AE logs and SAE reports
	  ○ Grade the severity of the AE
	  ○ Assign attribution/causality
	• Ensure that AEs are managed appropriately by clinical staff per protocol
	• Ensure AEs and SAEs are promptly, accurately, and completely reported to the sponsor, the IRB, and any other applicable regulatory bodies or institutional committees
	• Summarize the overall assessment of any adverse events and any new information that becomes available for the annual IRB continuing review

Co-investigator	• Protect the safety of the subject • Document assessments from all clinical visits completely and accurately, including any protocol specific forms • Ensure that AEs are managed appropriately by clinical staff per protocol • Report SAEs promptly, accurately, and completely to the PI and sponsor
APN/CRC	• Screen for AEs on an ongoing basis using patient-reported history, physical examination, laboratory data, chart review, and other available data for each subject enrolled in a clinical trial • Be aware of sponsor, IRB, and, as applicable, DSMC, DSMB, and FDA reporting guidelines and timelines • Notify PI as soon as an SAE is identified • Act as a patient advocate to protect the safety of the subject • Report SAEs promptly and completely in OnCore • Ensure reports are submitted to the sponsor, IRB, and other applicable committees or agencies within the required deadlines • Obtain internal and external medical records as needed to report the event(s) • Communicate with infusion staff and other members of the clinical team • Review the procedures mandated in the protocol for the clinical management of AEs with the PI • Maintain an AE log that is regularly reviewed by the PI for accuracy, including the assessment of severity and causality

	• File a copy of the SAE report in the patient's research chart.
Data Manager	• Record AE information in the Case Report Form in a timely manner
Regulatory Coordinator	• Submit reportable local SAE reports to the IRB of record, track the submission, and file the submission documents and IRB acknowledgement letter in the regulatory file • Submit SAEs to the DSMC, DSMB, and other entities as outlines in the study DSMP, as applicable • Submit reportable SAEs to the FDA for investigator held INDs and IDEs. o For an unexpected fatal or life threatening event that is associated with the drug, notify the FDA as soon as possible, but no later than 7 calendar days of receipt of the information by phone or fax o Information from lab animals that may suggest a risk to human subjects, notify the FDA as soon as possible, but no later than 15 calendar days after initial receipt of the information. Submit a written report on Form FDA 3500A (Med Watch)

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

ATTACHMENT B

University of Illinois Cancer Center | Clinical Trials Office

Adverse Event and Serious Adverse Event IRB Reporting Timelines
Local Adverse Events (AEs)

	UIC IRB		CIRB		WIRB	
Type of Reportable Event	**Timeline**	**Definition**	**Timeline**	**Definition**	**Timeline**	**Definition**
Serious Adverse Event	Within 5 business days of knowledge	Must be 1. Unanticipated a. Not outlined in protocol, IB, or ICF 2. Serious a. Death b. Life threatening injury c. Hospitalization d. Prolonged hospitalization e. Results in disability/incapacity f. Cause congenital/birth defects	Within 7 days of knowledge	Must have all 3 1. Unexpected, given the protocol, IB, or ICF 2. Reasonable possibility the incident has been caused by the research 3. Subjects are at greater risk of harm than previously known	Within 5 days	- New or increased risk - Adverse Events or IND safety reports that require a change to the protocol or consent - Unanticipated adverse device effect

	UIC IRB		CIRB		WIRB	
Type of Reportable	**Timeline**	**Definition**	**Timeline**	**Definition**	**Timeline**	**Definition**
AE, Local	Within 15 business days of knowledge	Unanticipated and, while not meeting the criteria of serious, indicates research is associated with a greater risk of harm to participants or others than previously known	Within 14 days of information being received	If related to other potential unanticipated problems	NA	
Adverse Event, External Includes AEs where the UIC IRB is not the IRB of record	Within 15 business days of knowledge	Unanticipated ,indicates research associated with greater risk of harm to subjects or others than previously known and more likely than not to have been caused by the procedures associated with or subject's participation in the research An analysis from the sponsor Coordinating Center or DSMC supporting that the event or problem is unanticipated, possibly related to the research, and is associated with a greater risk of harm to participants or others than previously known must be submitted with the report	Within 10 working days of information being received	If related and unexpected	N/A	

	Stroger IRB		RUSH IRB	
Type of Reportable Event	**Timeline**	**Definition**	**Timeline**	**Definition**
Internal Serious Adverse Event, Local	Within 7 days of information being received	Report if have all 3 1. Unexpected, given the protocol, IB, or ICF 2. Reasonable possibility the incident have been caused by the research 3. Subjects are at greater risk of harm than previously known	Within 10 days of knowledge	Report if have all 3: 1. Unanticipated 2. Serious 3. Require significant changes to protocol
Serious internal unanticipated event	Within 48 hours		Immediately	- Events from gene transfer studies - Also report to Biosafety Committee
External unanticipated events	Within 14 days of information being received		Within 10 working days of information being received	If related and unexpected

*The UIC IRB defines “external” as AEs that occur on studies for which the UIC IRB **is not** the IRB of record. For the purposes of this SOP, “external” **does not** refer to sponsor safety reports.

- CIRB: SOP, Section10.2 and 10.3
- WIRB: Guide for Researchers, Section 13
- Stroger: Guide for Investigators, Pages 54-56
- Rush: Per CIRB SOP, Section10.2 and 10.3
- Rush:: Reporting and Review of Unanticipated Problems Policy and Procedure

Appendix 8: SCON13 Reporting Unapproved Protocol Deviations

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

University of Illinois Cancer Center | Clinical Trials Office			
Standard Operating Procedure			
STUDY CONDUCT (SCON) **SCON13 Reporting Unapproved Protocol Deviations**			
SOP Number:	SCON13	**Effective Date:**	06/24/2020
Last Reviewed:	06/24/2020	**Policy Applies to:**	All Employees
Approval		**Responsibility**	
Cancer Center Approval Date: Title: CTO Administrative Director Approval Signature: _____		Responsibility for review and maintenance of this policy is assigned to: CTO Administrative Director Author and/or Designee: Darlene Kitterman, CTO Administrative Director	

POLICY OVERVIEW

This policy outlines the steps to follow for documenting and reporting reportable protocol deviations at the University of Illinois Cancer Center and the Clinical Trials Office (CTO).

BACKGROUND

Subject safety is the highest priority during the conduct of a clinical trial. Investigators are required to report deviations from the protocol to the study sponsor and the IRB. The PI may delegate this task to another qualified individual involved in the trial, such as a Co-investigator, but may not delegate responsibility.

RESPONSIBLE PERSONNEL

A. Advanced Practice Nurse (APN) on the Pediatric Services team
B. Clinical Research Coordinator (CRC)
C. Co-investigator
D. Data Manager (DM)
E. Principal Investigator (PI)
F. Regulatory Coordinator (RC)
G. Clinical Research Manager (CRM)
H. Regulatory Manager (RM)
I. Data and Safety Monitoring Committee (DSMC)

DEFINITIONS

A. **CAPA** – Corrective and preventative action is a planned improvement to an organization's processes taken to eliminate causes of non-compliance or other undesirable situations.
B. **Protocol Deviation** – Any deviation from the procedures or treatment outlined in the protocol document or regulatory requirements. Also known as a protocol "violation". Not all deviations are reportable.
C. **Protocol Exception** - A planned change to the research involving a single subject or, less commonly, a small group of subjects and is not a permanent revision to the research protocol.
D. **Major Protocol Violation** - A protocol deviation that causes harm to subjects or others, place them at increased risk of harm, impact the scientific integrity of the research, compromise the human subject protection program, have the potential to recur or represent possible serious or continuing non-compliance Major protocol violations may represent an unanticipated problem (particularly when unintentional) and/or potential serious noncompliance and require prompt reporting.

PROCEDURE

1. **Protocol Deviation Identification, Documentation, and Reporting**
    a. Refer to SOP SCON12 AE/SAE Documentation & Reporting and Attachments B through D to determine if the protocol deviation is reportable to the IRB of record.
    b. Examples of Reportable Deviations
        i. Missed study visits or procedures (e.g., laboratory test, CT scan) if poses a risk to the subject
        ii. Study drug dosing error
        iii. Enrollment of an ineligible subject
        iv. Consent form error (e.g., failure to re-consent a subject)
    c. Site staff and/or sponsor representative identifies the protocol deviation.
    d. The APN/CRC promptly requests additional information/medical records as needed for reporting purposes.
    e. The APN/CRC will promptly report all deviations the protocol requires to be reported to the study sponsor as soon as possible after learning of the event. Consult the protocol and sponsor for specific requirements regarding method and timeliness of reporting.
    f. The APN/CRC enters the deviation into OnCore within 2 business days of notification (See Attachment A, UICC CRC Protocol Deviation Reporting Procedure for additional details).
        i. If the subject was harmed or was at immediate risk of harm, call the study RC and inform them of the deviation immediately.
        ii. Complete the "Date Discovered," "Reported By," "Deviation Date," "Category", and "Description of Deviation" fields in the OnCore PD report.

iii. Print the report, attach a deviation sticker, and provide the report to the PI to assess the PD. This can also be done via email if necessary. Please see Attachment A for deviation sticker questions.
iv. If PI answers “yes” to any of the questions on the deviation sticker, CRC updates the deviation in OnCore by adding the PI assessments into the “Description of Deviation". This triggers OnCore to send out an email to the lead CRC, lead RA, lead DM, and clinical and regulatory managers that a deviation has been submitted.
v. File the signed deviation report in the subject chart.

g. The RC will determine whether the deviation is reportable or not and update Oncore.
h. If the study is a UIC investigator initiated clinical trial and the deviation is a Major Protocol Deviation, the RC will report the deviation to the DSMC or, in the case of a phase III UIC investigator initiated clinical trial, to the DSMB, and as necessary to others as outlined in the study Data and Safety Monitoring Plan (DSMP).
i. The RC will obtain the report from OnCore. If the event is determined to be reportable to the IRB of record, the RC will:
    i. Notify the CRM and RM who will formulate the Corrective and Prevention Action Plan (CAPA) for the IRB prompt report
    ii. The RC will report the event to the IRB of record and document the submission in OnCore.
j. After IRB acknowledgement is received, the RC will properly file all documentation, and inform the study team of any IRB required actions resulting from the deviation.

2. Protocol Exceptions

a. Externally sponsored studies
    i. Protocol exceptions for externally sponsored studies will not be implemented without prior sponsor approval. The PI should contact the study sponsor to request that an exception be made.
    ii. If the sponsor grants the exception, the CRC will document the decision of the sponsor for the exception in writing and file in the subject’s chart.
b. The CRC will notify the regulatory coordinator of the exception with the following information:
    i. Patient #
    ii. What the exception is and the rationale
    iii. Expected visit date
    iv. Documentation from sponsor approving exception, if applicable
c. The regulatory coordinator will submit the exception request to the IRB of record.
d. If the exception is being reviewed by the UIC IRB and approval is needed within a week, once the PI has submitted the exception to OPRS, the regulatory coordinator will:
    i. Contact the director of the study’s assigned IRB
    ii. Once receipt of the exception request has been verbally confirmed by the IRB director, the regulatory coordinator will wait 24 hours prior to the expected visit date
    iii. If no IRB approval, the regulatory coordinator will re-contact the IRB.

REFERENCE(S) / RELATED POLICY(IES)

SOP SCON12 AE/SAE Documentation and Reporting

COLLABORATION

This policy was developed in collaboration with the following Departments:
University of Illinois Cancer Center, Clinical Trials Office (CTO)

ATTACHMENTS

A. UICC CTO CRC Protocol Deviation Reporting Procedure
B. Deviation IRB Reporting Timelines
C. Protocol Exception Flow Chart
D. Protocol Deviation Flow Chart

ATTACHMENT A

UICC CTO CRC Protocol Deviation Procedure

- When a deviation is discovered, enter it into OnCore. If the subject was harmed or was at immediate risk of harm, call the study Regulatory Coordinator and inform them of the deviation immediately.
- Only fill out the "Date Discovered," "Reported By," "Deviation Date," "Category," and "Description of Deviation" fields.
- Print out the deviation report and attach a deviation sticker (see Figure 1 below). They are hanging on the door in clinic. If none are printed, the template can be found the K drive (K:\Clinical Team\Common Sheets\Avery8164ShippingLabels – Deviation Sign Off 2019-06-12).
- Have the PI assess the four categories, sign/date. Note: if PI not available to sign off in a timely fashion, please have them assess categories via email and print/file the email with the deviation report.
- Free text additional responses in Oncore to all of the categories in the "description of deviation" box and submit. Example: Patient consumed caffeine on PK day. Per PI deviation does not cause harm to subjects or others, does not place subjects at increased risk, and is not likely to recur or represent an unanticipated problem. This does affect scientific integrity of research, as it affects the primary study endpoint
- If PI answers "no" to all four categories, you do not need to enter anything more into OnCore. File the signed deviation report in the subject chart.

Figure 1: Protocol Deviation Sticker

Circle One

Yes No Causes harm to subjects or others

Yes No Places subjects at increased risk

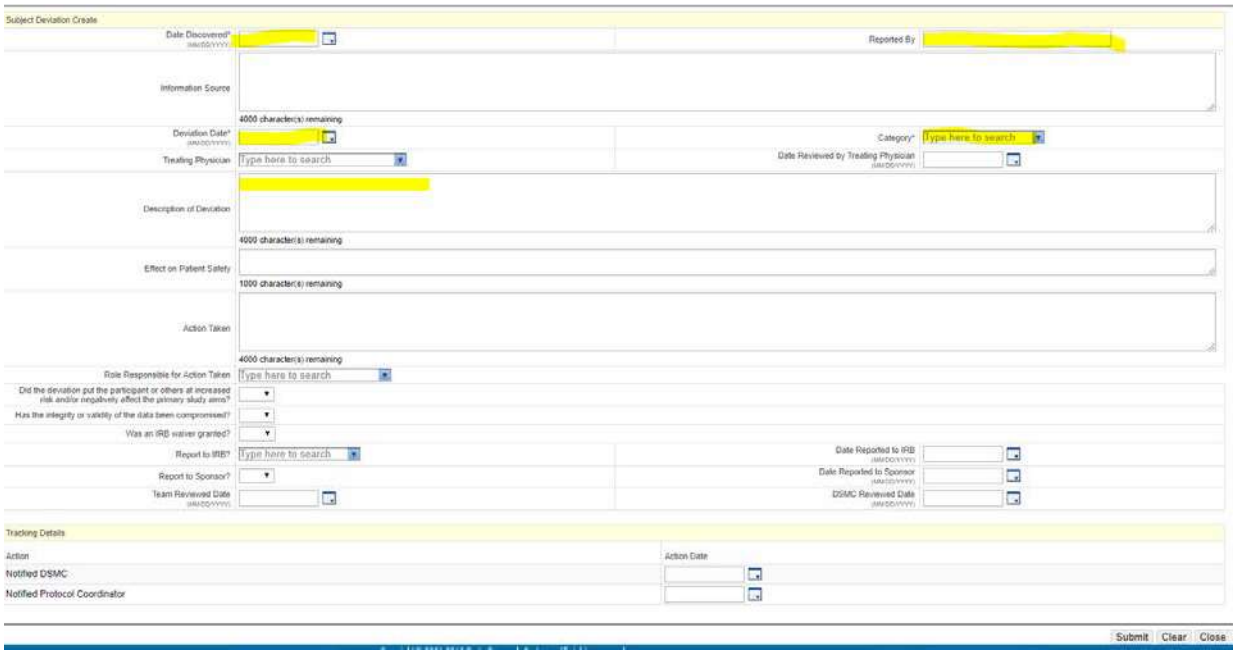
Yes No Affects scientific integrity of

Yes No Likely to recur or represents an unanticipated problem

PI Signature:_____

Date: _____

Figure 2: OnCore Protocol Deviation Report



Please Note: deviations often have reporting timelines, so please go through the above steps as quickly as possible if you think something might be considered reportable.

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

ATTACHMENT B

University of Illinois Cancer Center | Clinical Trials Office

Deviation IRB Reporting Timelines

	UIC IRB		CIRB		WIRB	
Type of Reportable Event	**Timeline**	**Definition**	**Timeline**	**Definition**	**Timeline**	**Definition**
Deviation/Violation	Within 5 business days of knowledge	Major protocol violations (Must be 1 of the following): 1. Cause harm to subjects 2. Place subjects at increased risk of harm 3. Impact scientific integrity of research 4. Compromise human subject protection 5. Have the potential to reoccur or present possible non-compliance	Within 7 days of knowledge	If the investigator believes the deviation or violation represents a potential problem (not outlined in the protocol or IB)	Within 5 days	Harmed a subject or placed subject at risk of harm Deviation made without IRB approval to eliminate an immediate hazard to a subject Breach of confidentiality Incarceration of a subject in a research study not approved to involve prisoners Unresolved subject complaint State medical board actions
Serious Non-Compliance	Within 5 business days of knowledge	Non-compliance that results in harm or risk of harm to the safety, rights or welfare of subjects	Within 7 days	Adversely affects the rights and welfare of study participants or results in any untoward medical occurrence that meets the criteria of “serious” or significantly impacts the integrity of study data	Within 5 days	Allegation of Noncompliance or Finding of Noncompliance

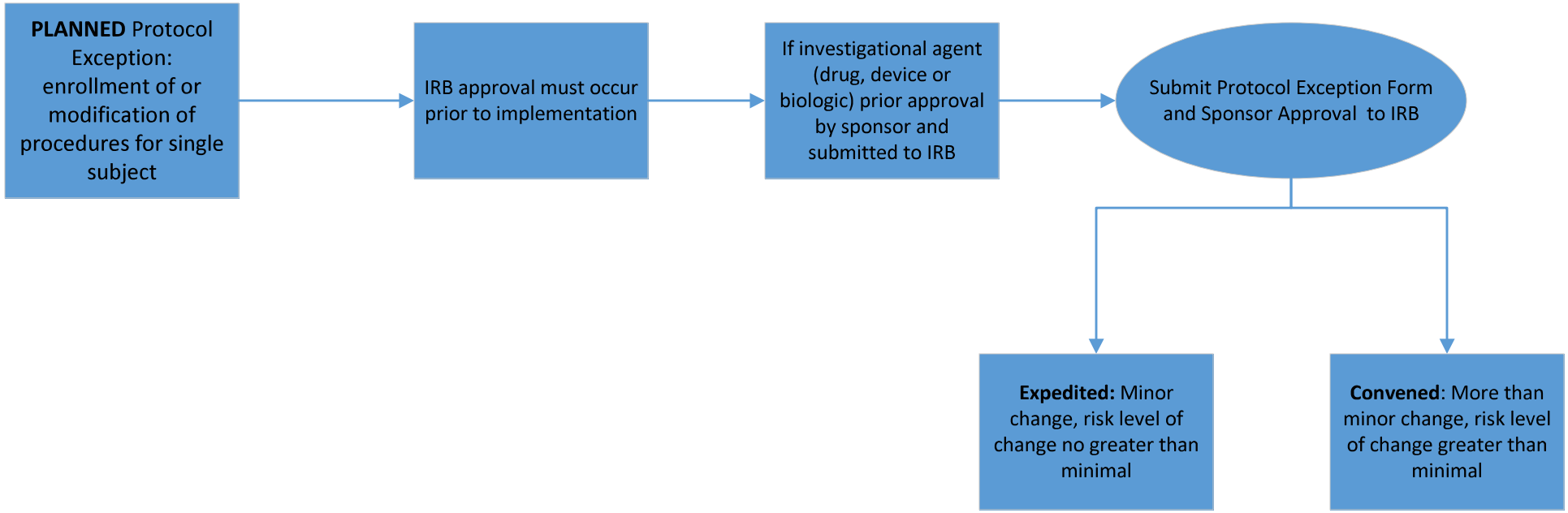
	Stroger IRB		RUSH IRB	
Type of Reportable Event	**Timeline**	**Definition**	**Timeline**	**Definition**
Deviation/Violation	Within 7 days of knowledge	If the investigator believes the deviation or violation increases risk to subject	Within 7 days of knowledge	If the investigator believes the deviation or violation represents a potential unanticipated problem (not outlined in the protocol or IB
	Continuing Review	If the investigator believes the deviation or violation does not increase the risk		
Serious Non-Compliance	Within 7 days of knowledge	Adversely affects the rights and welfare of study participation or results in any untoward medical occurrence that meets the criteria of "serious" or significantly impacts the integrity of study data	Within 7 days	Adversely affects the rights and welfare of study participants or results in any untoward medical occurrence that meets the criteria of "serious" or significantly impacts the integrity of study data

- CIRB: SOP, Section10.2 and 10.3
- WIRB: Guide for Researchers, Section 13
- Stroger: Guide for Investigators, Pages 54-56
- Rush: Per CIRB SOP, Section10.2 and 10.3

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

ATTACHMENT C

Protocol Exception Flow Chart



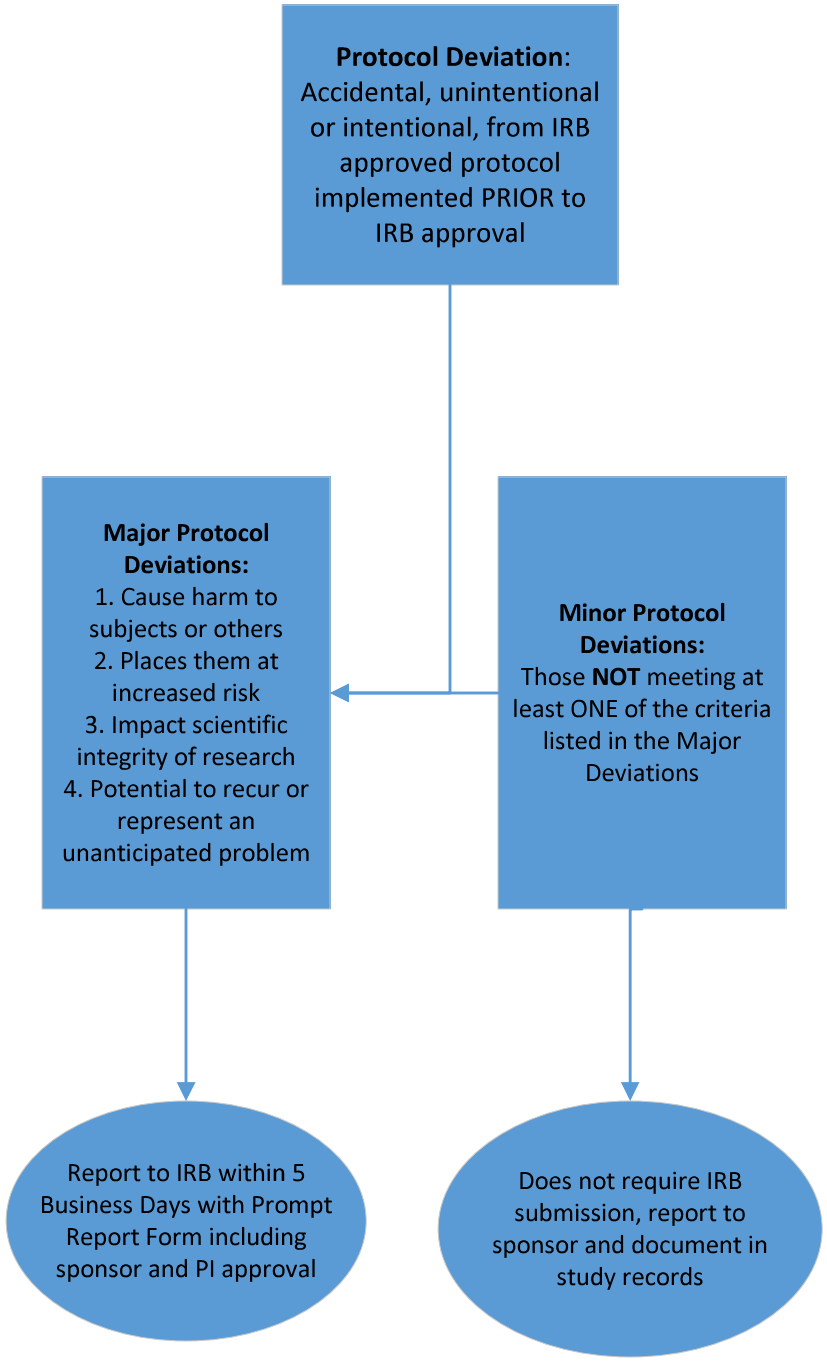
If you need a protocol exception AFTER the procedure has occurred; you must submit a Prompt Report for Non-Compliance AND a Protocol Deviation

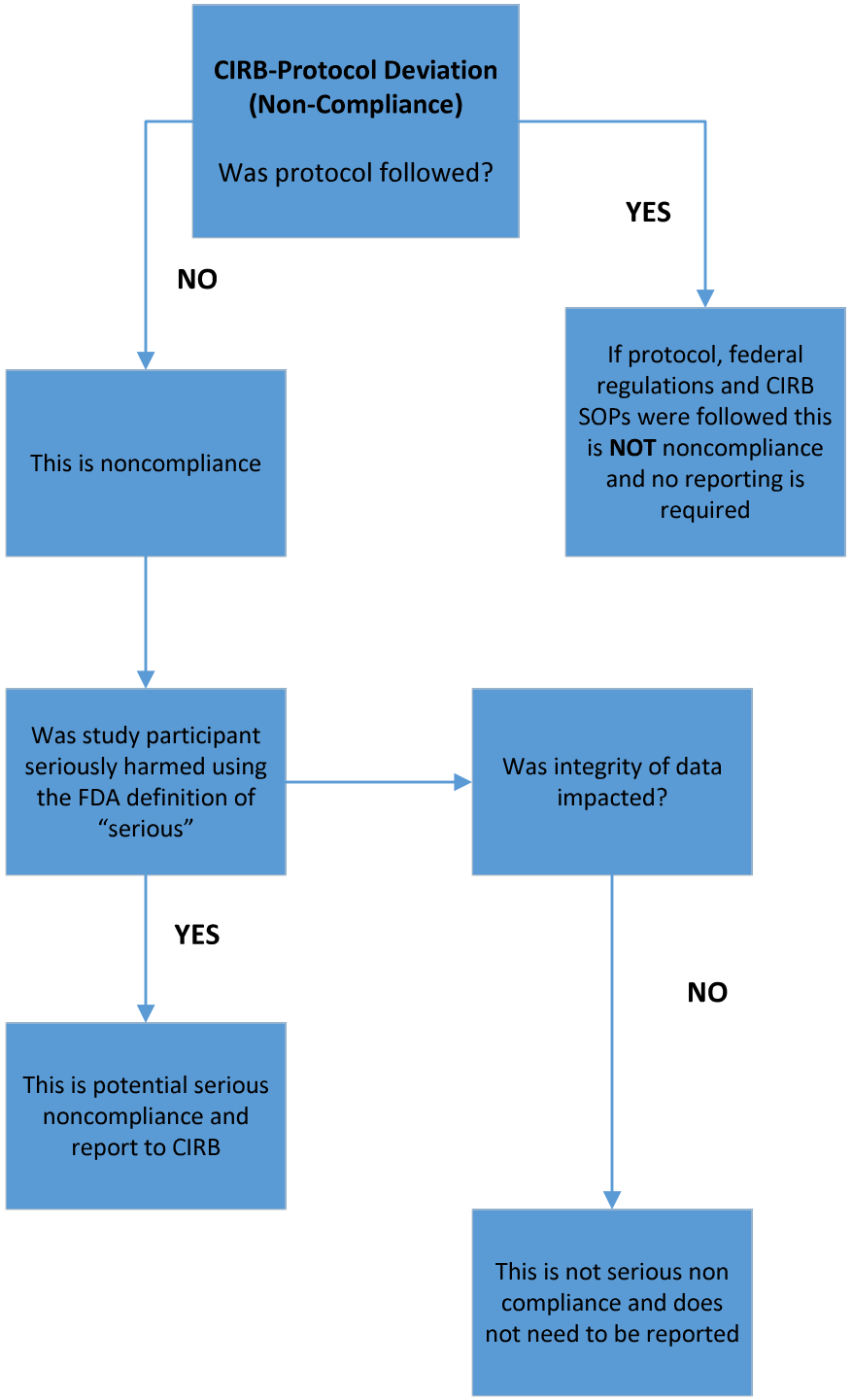
CIRB does not allow for planned protocol exceptions, AFTER the fact occurrences are deviations/ noncompliance GO TO Protocol Deviation Flowsheet

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

ATTACHMENT D

Protocol Deviation Flow Chart


Protocol Deviation: Accidental, unintentional or intentional, from IRB approved protocol implemented PRIOR to IRB approval
Major Protocol Deviations: 1. Cause harm to subjects or others 2. Places them at increased risk 3. Impact scientific integrity of research 4. Potential to recur or represent an unanticipated problem
Minor Protocol Deviations: Those **NOT** meeting at least ONE of the criteria listed in the Major Deviations
Report to IRB within 5 Business Days with Prompt Report Form including sponsor and PI approval
Does not require IRB submission, report to sponsor and document in study records


CIRB-Protocol Deviation (Non-Compliance)
Was protocol followed?
NO
YES
This is noncompliance
If protocol, federal regulations and CIRB SOPs were followed this is **NOT** noncompliance and no reporting is required
Was study participant seriously harmed using the FDA definition of "serious"
Was integrity of data impacted?
YES
NO
This is potential serious noncompliance and report to CIRB
This is not serious non compliance and does not need to be reported

Appendix 9: SCON18-1 Internal Monitoring & Auditing

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

University of Illinois Cancer Center | Clinical Trials Office			
Standard Operating Procedure			
Study Conduct (SCON) **SCON18 Audits** **SCON18-1 Internal Monitoring & Auditing**			
SOP Number:	SCON18-1	**Effective Date:**	06/25/2018
Last Reviewed:	07/05/2023	**Policy Applies to:**	All Employees
Approval		**Responsibility**	
Cancer Center Approval Date: Title: CTO Administrative Director Approval Signature: _____		Responsibility for review and maintenance of this policy is assigned to: CTO Administrative Director Author and/or Designee: Annette Kinsella, Quality Assurance & Education Specialist, CTO	

POLICY OVERVIEW

This policy outlines the procedure for preparing for, performing, and responding to internal monitoring and auditing, in accordance with GCP 4.9.7, at the University of Illinois Cancer Center's Clinical Trials Office (CTO).

BACKGROUND

Internal monitoring and auditing provides a systematic and independent examination of trial-related activities and documents to determine whether study data were generated, collected, analyzed, and reported per the protocol, SOPs, and applicable regulations. The purpose of these reviews is to ensure subject safety, verify the accuracy of data, identify problems, and implement corrective actions, as necessary.

Internal quality assurance (QA) monitoring and auditing activities may occur as part of the Clinical Trials Office's research QA program or in conjunction with any system level research QA program or initiative. Most internal reviews will be conducted by the QA/Education Specialist from the Cancer Center's CTO.

All active protocols are eligible for auditing and monitoring.

RESPONSIBLE PERSONNEL

A. Associate Director, Clinical Research (ADCR)
B. Clinical Manager
C. Clinical Research Coordinators (CRC)
D. CTO Administrative Director (CTO AD)
E. CTO QA/Education Specialist
F. Data Manager (DM)
G. Principal Investigator (PI)
H. Regulatory Coordinator (RC)
I. Regulatory Manager (RM)
J. Research Pharmacist

DEFINITIONS

A. **Audit –** A systemic and independent examination to determine whether research related activities conducted, data recorded, analyzed, and reported is in compliance with factors including, but not limited to: the study protocol, applicable state and federal guidelines and regulations, local/sponsor standard operating procedures, and Good Clinical Practices Standards. For the purposes of this SOP, internal audit and monitoring are used synonymously with "audit".
B. **Audit report –** A formal opinion, or disclaimer thereof, issued in writing by either an internal auditor or an independent external auditor as a result of an internal or external audit or evaluation performed.
C. **Exit Interview –** A meeting between the auditor(s) and study team held at the conclusion of the audit/inspection.
D. **Good Clinical Practice (GCP) –** GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.
E. **Institutional Review Board (IRB) –** An independent body constituted of medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, or protocol amendments, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
F. **Quality Assurance (QA) –** All those planned and systemic actions that are established to ensure that the trial is performed and the data are generated, documented, and reported in compliance with GCP and the applicable regulatory requirements.
G. **Standard Operating Procedures (SOPs) –** Detailed, written instructions to achieve uniformity of the performance of a specific function.
H. **National Clinical Trials Network (NCTN) -** NCI's National Clinical Trials Network is a collection of organizations and clinicians that coordinates and supports cancer clinical trials at more than 3,000 sites

across the United States and Canada. The NCTN provides the infrastructure for NCI-funded treatment, screening, and diagnosis trials to improve the lives of patients with cancer.

PROCEDURE

1. **Quality Assurance Program Protocol Selection**
    a. All UICC NCTN prospective registries and therapeutic studies, institutional interventional studies, and CTO managed prospective registries will be internally audited by the CTO QA/Education Specialist at the frequencies listed below.
        i. NCTN prospective registries and therapeutic studies: Audit every 6 months from activation date.
        ii. Institutional interventional studies: Audit quarterly from activation date, unless externally monitored. If no subjects have been enrolled, audit regulatory e-binder every 6 months.
        iii. Institutional prospective registries managed by CTO: Audit every 6 months from activation date, unless externally monitored.
2. **Schedule the Audit Visit**
    a. The QA Education Specialist will notify the PI, CRC, DM, RC and Research Pharmacist, if applicable, of the internal audit and schedule the audit within 4 weeks.
        i. The QA Education Specialist will confirm to all appropriate staff via email the audit date, time and the reason for the audit.
        ii. At the time of notification, the QA Education Specialist will provide a list of the cases selected for audit.
3. **Prepare for the Audit –** The most effective way to prepare for an internal audit is to maintain research documents in a compliant and thus "audit ready" condition at all times. Generally, internal auditors will provide up to a month notice (Refer to Attachment A for guidance on hosting internal audits).
4. **For external sites of investigator initiated clinical trials, remote access to the Electronic Medical Record (EMR), regulatory binder and Investigational Product documentation will be requested at the frequencies noted for investigational studies.**
    a. The CRC and/or DM will perform the following audit preparation duties:
        i. Retrieve all documents that may be reviewed by the auditor(s). These include, but are not limited to:
            1. Original, signed consent/HIPAA forms
            2. Case Report Forms (CRFs)
            3. Documents stored electronically in the research shared drive
            4. Research subject charts
            5. Source documents
            6. Hard copy films/scans and results
            7. Subject diaries and/or questionnaires
        ii. Review all necessary documents for accuracy, completeness, and proper organization, including screening and enrollment logs.
        iii. Re-review the protocol for any deviations, serious adverse events, queries, etc. that may be questioned during the audit.
        iv. Review all previous auditing/monitoring reports and correspondence to ensure that all corrective actions have been completed and documented.
        v. Ensure all applicable subject CRFs are up-to-date, all source documents and notes to file are organized and accessible, and all outstanding data queries have been resolved.

vi. Device studies, if applicable:
1. Ensure all device records are complete prior to the audit.
2. File all packing slips, shipment receipts, and return receipts with study documents as required for the investigational device.

b. The RC will perform the following duties:
i. Retrieve all documents that may be reviewed by the auditor(s). These include, but are not limited to:
1. Site regulatory binder(s)
2. Documents stored electronically in the research shared drive
3. Training documentation
4. IRB approved consent forms (original and amendments)
5. Delegation of Authority logs
ii. Review all essential documents for accuracy, completeness, and proper organization, including all forms in the regulatory binder.
iii. Re-review all IRB submissions to ensure the appropriate approval documents are on file.
iv. Review all previous auditing/monitoring reports and correspondence to ensure that all corrective actions have been completed and documented.
v. Ensure the regulatory binder is up-to-date prior to the audit, including any relevant sponsor communication.

c. The Research Pharmacist will perform the following duties, as applicable (*Note: device IP duties are the responsibility of the CRC*):
i. Retrieve all documents that may be reviewed by the QA/Education Specialist. These include, but are not limited to:
1. Investigational Product (IP) accountability records
2. IP packing slips, shipment receipts, and return and/or destruction receipts
ii. Review all essential documents for accuracy, completeness, and proper organization.

5. Audit Conduct

a. Clinical Research Manager, with assistance from the CRC and/or DM
i. Will ensure all requested items are available for review.

b. QA Education Specialist
i. Will review the following:
1. Investigator initiated studies:
a. 100% subject ICFs and eligibility criteria
b. Subject source documents and CRFs
i. Random 50% of interventional study subjects
ii. Random 10% of non-interventional study subjects
c. 100% of regulatory documents
d. Random 50% of subject Investigational Product (IP) accountability records
2. NCTN studies:
a. 100% ICFs and eligibility criteria
b. Subject source documents and CRFs: Random 25% or 2 study subjects, whichever is greater
c. 100% of regulatory documents including assuring all amendments processed and correct ICF version and language used
d. Random 25% or 2 whichever is greater of subject IP accountability records

c. If an issue is uncovered during the audit, a greater % of source documents and CRFs can be reviewed.
d. Exit Interview
    i. The following individuals will participate in the Exit Interview: PI, CRC, DM, and Research Pharmacist (if applicable). A separate meeting may be held with the PI, if they are not available immediately after the audit.
    ii. The Exit Interview will be held at the conclusion of the audit.
    iii. QA Education Specialist
        1. Will conduct exit interview
        2. Review and discuss audit findings.
        3. Provide a summary of key findings and action items to the study team.

6. Audit Follow-Up

a. Quality Assurance and Education Specialist
    i. Within 4 weeks of the audit a written report of the audit results will be completed (refer to Attachment D, Quality Assurance Audit Report Template)
    ii. Send the signed audit report to the PI, CRC, RC, and, if there are findings, to the CRM, RM, and CTO AD.
    iii. If performing monitoring on behalf of the UICC DSMC, distribute the audit report as specified in the UICC DSMP.
    iv. Within 24 hours of receipt of audit report, the CTO AD will communicate significant findings (e.g. actionable finding(s)) to the CTO MD and ADCR. The ADCR will determine if findings should be distributed to the Department Chair of the PI.
b. Clinical Research Manager and RM:
    i. If a corrective action plan is requested by the QA/Education Specialist:
        1. Work with the PI to draft a preliminary response and corrective action plan (if necessary) within the timeframe specified on the audit report. (See Attachment B, Guidance On Responding to Audit Findings and Attachment C, Corrective and Preventive Action Plan Template.)
        2. Obtain PI signature on the final audit response.
        3. Provide the audit response to the QA/Education Specialist, with a copy to the CTO AD, the CTO MD, the ADCR, the RC, and the PI.
        4. Maintain all documentation associated with the audit including correspondence, report of audit findings, and the audit response in the shared drive.
c. RC:
    i. Upon receipt of the audit report and, if required, the corrective action plan, submit the documents to the IRB of record and file the IRB acknowledgement letter in the shared drive.
    ii. When applicable, submit the documents to the DSMC and file all correspondence in the shared drive.

REFERENCE(S) / RELATED POLICY(IES)

GCP 4.9.7
UICC Data and Safety Monitoring Plan

COLLABORATION

This policy was developed in collaboration with the following Departments:
University of Illinois Cancer Center, Clinical Trials Office (CTO)

ATTACHMENTS

A. Guidance on Hosting Internal Audits
B. Guidance on Responding to Audit Findings
C. Corrective and Prevention Action Plan Template
D. Quality Assurance Audit Report Template

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

ATTACHMENT A

University of Illinois Cancer Center | Clinical Trials Office

Guidance on Hosting Internal Audits

Preparing for an Internal Audit:
The most effective way to prepare for an internal audit is to maintain the research documents in a compliant and thus "audit ready" condition at all times. Generally, internal auditors will provide up to a month notice.

During the Audit:

- Set the proper tone. Be available, maintain a professional, cordial, and cooperative demeanor at all times. Do not, under any circumstances, become defensive or argumentative.
- Have medical records, research charts, and source documents available and provide only those specifically requested.
- During the audit, it is likely the auditor will make "observations" relating to the conduct of the trial, documentation, etc. The CRC overseeing the audit will work with the research team, making every effort to address and correct these observations while the audit is taking place.
- If you are not sure how to answer a question or do not feel comfortable answering a question, it is appropriate to say, "I will get back to you". Then seek advice from the CRC overseeing the audit, the CTO AD, or other appropriate personnel on how to address the question.

The Exit Interview:

- During the Exit Interview, politely identify for the auditor all observations addressed and/or corrected during the audit.
- If any observation noted deals with not meeting regulations, carefully point out that the regulations are subject to interpretation. Then explain your intentions and, if true, how your actions protected the subject(s).
- If you can clearly identify an appropriate corrective action in response to an observation, indicate what measures you plan to take to correct the observation immediately. **Do not** commit to a future action that you do not intend to make or are unable to fulfill.

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

ATTACHMENT B

University of Illinois Cancer Center | Clinical Trials Office

Guidance on Responding to Audit Findings

Formulating an Appropriate Response:

- Carefully review the audit report and ensure that you understand and are familiar with any deficiencies cited. Think critically about each violation and what circumstances led to its occurrence.
- For violations involving regulatory requirements or data management, it should be determined why the information is missing or discrepant and the information should be recovered and added when possible. The response to these types of violations should include information regarding how the violation was addressed and include a corrective action plan to ensure this type of violation will not be repeated in the future.
- If a violation involves failure to conduct protocol specific procedures (i.e., treatment administration, blood draws, recording vital signs, tissue sampling, drug accountability), investigate why the procedure was not completed and in addition to describing the circumstances that may have prevented protocol compliance, also provide a corrective and preventative action plan (CAPA) that will ensure systemic changes are implemented to prevent the problem from recurring.
- The response to audit findings is a formal communication and should be in memo or letter format.
    - Be clear and concise in the reply.
    - Use the audit report as an outline in formulating your response.
    - It is not acceptable to insert your response into the audit report.
    - Do not use shading or highlighting of any kind in your response to avoid text being obscured during photocopying.

ATTACHMENT C

Corrective and Prevention Action Plan Template

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

Example of a Corrective and Preventive Action (CAPA) Plan

CORRECTIVE AND PREVENTATIVE ACTION PLAN

Protocol:
CRC:
Principal Investigator:
Date of Report:

Section I

Identified Issue:

Evaluate the extent of the problem.

- *Document a brief description of the issue(s)*
- *How many subjects were impacted?*
- *Was any subject harmed or could have been harmed?*
- *Could this problem exist in other protocols that use the same processes and or procedures and staff?*

Section II

Causal Analysis:

What is the root cause?

- *Describe the reason the incident(s) occurred*
- *Investigate how and why the incident(s) occurred*
- *Is there multiple causes?*
- *Is it lack of trained staff?*
- *Is it processes and or procedures?*
- *Is it both?*

Section III

Corrective Action:

What are the resolutions?

- *Describe the corrective actions taken or planned*
- *Indicate who will perform the corrective actions and the timeframe for implementation*
- *Describe the processes and or procedures developed to prevent the problem in the future*

Section IV

Documentation of Staff Retraining (If Applicable):

Document the retraining of staff on the new processes and or procedures

Members Required to Attend Retraining
Attach Attendance Sheet with Minutes

Section V

Evaluation:

Describe follow-up and evaluation of the effectiveness of the new processes and or procedures

- *Document the timeframe for the evaluation*
- *Document who will be responsible for this evaluation*
- *Confirm that the new processes and or procedures have corrected the problem(s)*
- *Document that the problem(s) have been corrected*
- *Document the timeframe of re-reviewing our continued compliance of the processes and or procedures*

Event Reoccurrence:
Address reoccurrences and further preventative measures and retraining and process improvements

Section VI

Principal Investigator's Review of Corrective Action Plan and Acknowledgement of Continual Improvement:

I, Dr. <INSERT NAME> have read and agree with the CAPA plan and acknowledge my agreement to supervise and implement immediate corrective action to secure compliance.

_____ _____
Principal Investigator's Signature **Date of Review**

_____ _____
Corrective Action Plan Preparer's Signature **Date of Signature**

ATTACHMENT D

Quality Assurance Audit Report Template

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

Quality Assurance Audit Report

Protocol Title:	PI Name:	IRB #
Drug/Device:	Visit Date(s):	Visit Conducted By:

Site Visit Personnel List the study personnel who met with the Monitor during the visit (if not at all visit dates, specify date)
Name

Enrollment Status	
# of subjects approved by IRB	
Consented:	
Enrolled/Randomized:	
Ongoing:	
Completed:	
Discontinued:	

Auditing Activities Comment and/or Action Items required for all shaded answers.

General Site Information	Yes	No	NA	Comment
1. Were there any changes in facilities?				
2. Were there changes in study staff				
3. Did the QA Education Specialist meet with the PI to discuss the findings?				
4. Does the Principal Investigator continue to be involved in the study?				
5. Is IRB approval Current?				
6. Have there been any lapses in IRB approval?				
7. If yes, was any data collected during that time?				

ADMINISTRATIVE RECORDS

REGULATORY DOCUMENTS AND STUDY-RELATED FORMS				
Do any of the following documents require follow-up or revision?	**Yes**	**No**	**NA**	**Comment**
Study Personnel:				
8. FDA Form 1572 (IND studies) or Signed Investigator Agreements (IDE studies)				
9. Financial disclosures (signed form 3455) for all participating investigators				
10. Training documents (e.g. training on protocol, investigational product, data collection)				
11. Delegation of Authority Log				
12. CVs, licenses, certifications for all investigators/study personnel				
Protocol and Amendments:				

REGULATORY DOCUMENTS AND STUDY-RELATED FORMS				
Do any of the following documents require follow-up or revision?	**Yes**	**No**	**NA**	**Comment**
13. Current and Previous IRB approved protocols and amendments				
14. PRC CR and amendment approvals				
Investigational Drug Brochure/Package Insert/Device Manual:				
15. Current and Previous Investigational Drug Brochures/Package Inserts/Device Manuals				
Informed Consent:				
16. Current and Previous Consent/HIPAA Authorization Forms for IIT, WCG, Pharmaceutical Sponsored Study				
17. Spanish Consent/HIPAA Authorization Forms for WCG, Pharmaceutical Sponsored Study-if available				
18. NCI Current PVD Consent Document with Current Boilerplate Language				
19. NCI Current PVD Spanish Consent-if available on CTSU				
20. Spanish Short Form, if applicable				
21. Spanish HIPAA-NCI Studies				
IRB Documents/Correspondence:				
22. Initial Review Application and Corresponding Communications and Approvals				
23. Modification Applications and Corresponding Communications and Approvals				
24. Continuing Review Applications and Corresponding Communications and Approvals				
25. Other IRB approved protocol documents (e.g. advertisements, newsletters, questionnaires, diaries)				
26. Adverse Event Reports and Communications				
27. Protocol Deviation Reports and Communications				
28. IRB membership list				
FDA Correspondence (if PI is IND/IDE Sponsor-Investigator):				
29. 1571				
30. Initial IND/IDE submission				
31. Letter from FDA with IND/IDE#				
32. Annual Reports to FDA				
33. IND Safety Reports/UADE Reports				
34. Final Report (if applicable)				

REGULATORY DOCUMENTS AND STUDY-RELATED FORMS				
Do any of the following documents require follow-up or revision?	**Yes**	**No**	**NA**	**Comment**
35. Protocol Amendments				
36. Informational Amendments				
37. Reports of New Investigator				
38. Marketing Application (NDA/BLA/PMA if applicable)				
39. Financial Disclosure (form 3454) if marketing application has been filed				
40. Documentation re: Manufacturing Facilities if applicable				
General Correspondence:				
41. Correspondence related to the conduct of the study (e.g. between the manufacturer, PI, study staff, co-investigators)				
Lab/other Facilities:				
42. Laboratory/Equipment certification				
43. Lab normal ranges				
44. Documentation of Equipment Maintenance				
Subject Enrollment Records				
45. Subject Screening/Enrollment Log				
46. Subject Randomization Log				
47. Documentation of screen failures				
Study Reports (if applicable):				
48. DSMB Reports				
49. Clinical/Toxicology Reports from Manufacturer				

INVESTIGATIONAL PRODUCT RECONCILIATION:

Study Drug/Device	Yes	No	N/A	Comment
50. Was study drug/device inventory checked?				
51. Were there any problems with drug/device labeling?				
52. Is Investigational Product stored separately from similar commercially available product?				
53. Is the Investigational Product stored per the manufactures specifications?				
54. Are there any problems with drug/device expiration dates?				
55. Were the shipping records available and complete?				
56. Has any drug/device been returned or disposed of?				
57. Was the drug/device log complete?				
58. Are there any discrepancies between what was dispensed to and returned from the subject?				
59. Are there any problems with the dosing schedule?				
60. Have all new subjects been randomized correctly?				
61. Are there any problems with the blind?				

SUBJECT RECORDS:

Informed Consent/HIPAA	Yes	No	NA	Comment
62. Were informed consents/HIPAA authorizations present for all subject records reviewed?				
63. Did consent forms have appropriate signatures and dates?				
64. Were the correct versions of the consent/HIPAA forms signed by study subjects?				
65. Did subjects sign consent forms before any study-related assessments were done?				
66. Were subjects re-consented as required by the IRB?				
67. Informed consents/HIPAA Authorizations were checked for the following subjects:	☐ All			

Case Report Form/ Case History Review	Yes	No	NA	Comment
68. Are CRFs competed in a timely manner?				
69. Are CRFs completed correctly?				
70. Have research activities occurred per the IRB approved protocol?				
71. Do the source documents (e.g. medical history) support inclusion/exclusion criteria?				
72. Did the site receive prior approval for protocol deviations and were they adequately documented in the source and CRFs.				
73. Information on the CRFs was supported by source documentation				
74. Are Source Documents complete, logical, and available?				
75. Does the protocol identify data that will be recorded directly on the CRFs?				
76. Are there any issues with doses of study medication and/or concomitant medications?				
77. Were subjects provided the necessary instructions on how to use, store and return study medication?				
78. Subject death, withdrawals, dropouts, and subjects lost to follow-up are reported and explained adequately in the source and CRFs.				
79. Are authorized personnel making corrections correctly (e.g. legible original entries, initial and dated changes) to the source and CRFs?				
80. Were adverse events adequately documented and reported per the overseeing IRBs policy and/or FDA regulations, as appropriate?				
81. Were the all requested data clarifications made?				
82. Source documents for the following CRFs were reviewed ☐ All				

Subject #	Study Visits or CRF pages checked		Comment

ACTION ITEMS		
Action needed	**Repeat item**	**Date discussed**

Signature of person who conducted the visit

Date

Appendix 10: SCON18-2 External Auditing

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

University of Illinois Cancer Center | Clinical Trials Office

Standard Operating Procedure

Study Conduct (SCON)
SCON18 Audits
SCON18-2 External Auditing

SOP Number:	SCON18-2	**Effective Date:**	10/02/2018
Last Reviewed:	01/30/2023	**Policy Applies to:**	All Employees

Approval	Responsibility
Cancer Center Approval Date: Title: CTO Administrative Director Approval Signature: _____	Responsibility for review and maintenance of this policy is assigned to: CTO Administrative Director Author and/or Designee: Angela Allred, Huron Consulting Group

POLICY OVERVIEW

This policy outlines the procedure for preparing for and responding to external audits, in accordance with 21 CFR 312.68, Good Clinical Practice (GCP), National Clinical Trials Network (NCTN) policy, and other clinical trial consortia policy at the University of Illinois Cancer Center's Clinical Trials Office (CTO).

BACKGROUND

The FDA conducts routine and for cause clinical investigator inspections to ensure the protection of the rights, safety, and welfare of human research subjects and the quality and integrity of data submitted to the Agency. Local IRBs, such as the University of Illinois at Chicago IRB, may also conduct audits of trials under their purview. They also can conduct routine and for cause audits.

The FDA conducts both announced and unannounced inspections of clinical investigator sites, typically under the following circumstances: to verify the accuracy and reliability of data that has been submitted to the Agency; as a result of a complaint to the Agency about the conduct of the study at a particular investigational site; in response to sponsor concerns; upon termination of the clinical site; during ongoing clinical trials to provide real-time assessment of the

investigator's conduct of the trial and protection of human subjects; at the request of an FDA review division; and related to certain classes of investigational products that the FDA has identified as products of special interest in its current work plan (i.e., targeted inspections based on current public health concerns).

The Clinical Trials Monitoring Branch (CTMB) of the Cancer Therapy Evaluation Program (CTEP) in the DCTD, provides direct oversight of each Network Group's monitoring program which includes auditing as one component. The purpose of an audit is to document the accuracy of data submitted to the Network Groups and to verify investigator compliance with protocol and regulatory requirements. In addition, the monitoring program provides an opportunity for the audit team to share with the institution staff, information concerning data quality, data management, and other aspects of quality assurance. The major objective of the audit program used by the Network Groups is to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data with source documents. The NCTN Program requires all institutions to be audited at least once every 36 months. In addition, a 'for cause' audit may be warranted when there are concerns or irregularities found through quality control procedures or when allegations of possible scientific misconduct are made.

Research sponsors may also request a for-cause or routine audit, to ensure quality assurance compliance with the protocol, GCP, and other relevant state and federal guidelines and regulations. Sponsor audits may be conducted by the sponsor, or a third party designee, such as a Contract Research Organization (CRO).

External IRBs, such as central IRBs, may also conduct audits of trials under their purview.

RESPONSIBLE PERSONNEL

A. Lead Clinical Research Coordinators (CRC)
B. Associate Director, Clinical Research (AD-CR)
C. CTO Administrative Director (CTO AD)
D. CTO Medical Director (CTO MD)
E. Study Principal Investigator (PI)
F. CTO QA/Education Specialist
G. Data Manager (DM)
H. Principal Investigator (PI)
I. Study Regulatory Coordinator (RC)
J. CTO Assistant Director, Regulatory & Compliance (CTO Asst. D)
K. CTO Associate. Director, Clinical Operations (CTO Assoc. D)
L. Research Pharmacist

DEFINITIONS

A. **Audit** – A systemic and independent examination to determine whether research related activities conducted, data recorded, analyzed, and reported is in compliance with factors

including, but not limited to: the study protocol, applicable state and federal guidelines and regulations, local/sponsor standard operating procedures, and Good Clinical Practices Standards.

B. **Audit report** – A formal opinion, or disclaimer thereof, issued in writing by either an internal auditor or an independent external auditor as a result of an internal or external audit or evaluation performed.
C. **Clinical Trials Monitoring Branch (CTMB)** – Provides oversight of the NCI National Clinical Trials Network (NCTN) monitoring programs.
D. **Contract Research Organization (CRO)** – A CRO is an organization that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.
E. **Exit Interview** – A meeting between the auditor(s) and study team held at the conclusion of the audit/inspection.
F. **For-cause audit** – For-cause audits may be conducted if during the monitoring process a sponsor has continual documented accounts of possible noncompliance, data discrepancies, or concerns over the ethical conduct of the study by the investigator. The sponsor may contact the FDA and report these concerns which could result in a for-cause FDA inspection. Study participants could also contact the FDA to report suspected wrong-doing that may lead to a for-cause inspection. It is the responsibility of the Network Group/NCORP Research Base to immediately notify CTMB upon learning of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. The IRB and sponsor can also perform a for-cause audit.
G. **Good Clinical Practice (GCP)** – GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.
H. **Inspection** – A regulatory authority (such as the FDA) conducting an official review of documents, facilities, records, and any other resources that are deemed by the regulatory authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or CRO's facilities, or at other establishments.
I. **Institutional Review Board (IRB)** – An independent body constituted of medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, or protocols, and amendments, and of the methods and materials to be used in obtaining and documenting informed consent of trial subjects.
J. **Quality Assurance (QA)** – All those planned and systemic actions that are established to ensure that the trial is performed and the data are generated, documented, and reported in compliance with GCP and the applicable regulatory requirements.
K. **Sponsor** – A person or entity that initiates a clinical investigation of a drug or device – usually the manufacturer or research institution that developed the drug or device. The sponsor does not actually conduct the investigation, but rather distributes the new drug or device to investigators and physicians for clinical trials. The drug/device is administered/implanted to subjects under the immediate direction of an investigator who

is not also a sponsor. A clinical investigator, however, may serve as a sponsor-investigator. The sponsor assumes responsibility for investigating the new drug/device, including responsibility for compliance with applicable laws and regulations. The sponsor, for example, is responsible for obtaining FDA approval to conduct a trial and for reporting the results of the trial to the FDA.

L. **Standard Operating Procedures (SOPs)** – Detailed, written instructions to achieve uniformity of the performance of a specific function.

PROCEDURE

Note: The QA/Education Specialist plays a prominent role with external audits and is responsible for coordinating all audit activities.

1. **Notification of an External Audit/Inspection**
    a. Once notification of an upcoming external audit/inspection has been obtained, the PI (or person receiving the notification, if not the PI) will notify the Clinical Trials Office (CTO) immediately, via email to the CTO AD, AD-CR, CTO Assoc. D, CTO Asst. D-Regulatory and QA/Education Specialist.
    b. If notified of an audit or inspection by external regulatory authorities (i.e., FDA) or funders (i.e., NIH, DOD, etc.), the QA/Education Specialist will immediately notify the sponsor, the PI (if notification does not come from the PI), the CTO AD, the CTO MD, the AD-CR, the CTO Assoc. D, the CTO Asst.-D Regulatory, and the IRB.
2. **Schedule the Audit/Inspection Visit**
    a. The QA/Education Specialist will work with the external auditor to schedule the audit/inspection in conjunction with the PI.
    b. The QA/Education Specialist will ensure a meeting space is scheduled for the audit/inspection or, in the event of a remote audit, will set up a zoom meeting with the audit participants. The QA/Education will also assure the visit is added to the shared calendar.
        i. For in person audits, a conference room or other private meeting space must be used for the duration of the audit/inspection. The space should be free from distractions and without access to other study documents and/or patient records.
        ii. For the duration of in person audits/inspections, an office or conference room will also be designated as a “Ready Room”, where all relevant Case Report Forms (CRFs), source documentation, regulatory documents, accountability logs, etc. will be organized. This will ensure that auditor requests can be fulfilled in real-time.
    c. The QA/Education Specialist will notify appropriate staff members of the upcoming audit/inspection.
        i. The following staff members will be notified: CTO MD, CTO AD, AD CR, PI, CTO Asst. D- Regulatory, CTO Assoc. D, Lead CRCs, Study RCs, Lead DMs, Research Pharmacist (if applicable), other clinical research personnel as necessary, and any applicable representatives from other hospital departments.

ii. The following information will be conveyed in writing to the aforementioned staff members: audit date, time, location, purpose of the studies to be audited, audit/inspection, identity of the auditor(s), and audit itinerary if provided by auditors.

3. **Prepare for the Audit/Inspection** – The most effective way to prepare for an external audit/inspection is to consistently and routinely maintain research documents in a compliant and thus "audit ready" condition at all times. Generally, external sponsors provide up to a month notice, but the FDA or other regulatory agencies are only required to provide 24 hours of notice prior to the first day of the inspection.
    a. The PI will perform the following duties:
        i. Conduct a Pre-Audit Preparation Meeting with the study team (QA/Education Specialist, CTO Asst. D-Regulatory, CTO Assoc. D, Lead CRC, Study RC, Lead DM, Research Pharmacist and other personnel (if applicable) to review audit preparation and trial status and plan roles for the audit/inspection.
    b. The QA/Education Specialist will perform the following audit/inspection oversight duties:
        i. Oversee the audit/inspection preparation process to ensure the site is audit/inspection ready prior to the audit/inspection date.
        ii. At a minimum meet at least one time. Conduct a Pre-Audit Preparation/Readiness Meeting between the PI and the study team. Confirm that each area is prepared and assist in resolving any outstanding issues.
        iii. Work closely with each member of the study team during the audit/inspection preparation process to provide guidance and/or assistance as necessary.
        iv. Conduct preliminary mock audits as requested by the study staff.
    c. The CRC and/or DM will perform the following duties:
        i. Retrieve all documents that may be reviewed by the auditor(s). For NCTN audits, cases will be requested in advance. If the audit is remote, the DM will set up a HIPAA compliant box folder to file the electronic documents. Documents include, but are not limited to:
            1. Original, signed consent/HIPAA forms
            2. Case Report Forms (CRFs)
            3. Documents stored electronically in the research shared drive
            4. Research subject charts
            5. Source documents
            6. Hard copy films/scans and results
            7. Patient diaries and/or questionnaires
        ii. Review all necessary documents for accuracy, completeness, and proper organization, including screening and enrollment logs.
        iii. Re-review the protocol and any deviations, serious adverse events, queries, etc. that may be questioned during the audit/inspection.
        iv. Review all previous auditing/monitoring reports and correspondence to ensure that all corrective actions have been completed and documented.

v. Ensure all applicable subject CRFs are up-to-date, all source documents and notes to file are organized and accessible, and all outstanding data queries have been resolved.
vi. Device studies, if applicable:
    1. Ensure all device records are complete prior to the audit/inspection.
    2. File all packing slips, shipment receipts, and return receipts with study documents as required for the investigational device.

d. The RM/RC will perform the following duties:
    i. NCTN groups will provide a listing of studies that will be audited. The RM will email regulatory documents prior to the audit as instructed by the auditor.
    ii. RC will retrieve all documents that may be reviewed by the auditor(s). These include, but are not limited to:
        1. Site regulatory binder(s)
        2. Documents stored electronically in the research shared drive
        3. Applicable SOPs (as requested)
        4. Training documentation
        5. IRB approved consent forms (original and amendments)
        6. Delegation of Authority logs
        7. Monitoring logs
    iii. For NCTN audits, once the listing of studies is received that will be audited:
        1. RC will copy the documents requested by the auditor and scan them
        2. RM will email them to the auditor by the deadline provided
    iv. RC will review all essential documents for accuracy, completeness, and proper organization, including all forms in the regulatory binder.
    v. Re-review all IRB submissions to ensure the appropriate approval documents are on file.
    vi. RM will ensure the regulatory binder is up-to-date prior to the audit/inspection, including any relevant sponsor communication.
    vii. Review all previous auditing/monitoring reports and correspondence to ensure that all corrective actions have been completed and documented.

e. The Research Pharmacist will perform the following duties (*Note: device IP duties are the responsibility of the CRC*):
    i. Retrieve all documents that may be reviewed by the auditor(s). These include, but are not limited to:
        1. Investigational Product (IP) accountability records
        2. IP packing slips, shipment receipts, and return and/or destruction receipts
    ii. Review all essential documents for accuracy, completeness, and proper organization.
    iii. Review all previous auditing/monitoring reports and correspondence to ensure that all corrective actions have been completed and documented.

4. **Hosting the Audit/Inspection** (Refer to Attachment A for guidance on hosting audits/inspections)

a. Principal Investigator
    i. It is not necessary for the PI to be present during the audit/inspection, but he/she must be available onsite to answer any questions that arise.
    ii. Attend the Exit Interview at the conclusion of the audit/inspection.
b. CTO Administrative Director
    i. Attend the Exit Interview at the conclusion of the audit/inspection.
c. QA/Education Specialist
    i. If in person, meet the auditor(s)/Inspector(s) and if requested, provide a brief tour of the facility, only including areas requested by the auditor(s).
    ii. For regulatory agency inspections, the PI (or designee) will verify the inspector's credentials. **Do not** photocopy the inspector's credentials. Sign the Form FDA 482 (Notice of Inspection) and retain a copy.
    iii. Commence the meeting by introducing the study team and providing housekeeping information (e.g., restroom location, contact information for study staff).
    iv. Assemble and provide documents requested (do not provide or offer supplemental documentation. Only provide what is requested by the auditor(s)).
    v. Inform the auditor(s) that all requests for specific information or staff interviews will be coordinated through the QA/Education Specialist or delegate as appropriate.
    vi. Function as the auditor's escort for the duration of the audit/inspection; the QA/Education Specialist must be available to the auditor at all times.
    vii. Confirm with the auditor(s) his/her preference for handling issues and queries.
    viii. Acting as scribe, keep a written record of all audit related activities, including all document requests, requests for personnel interviews, or discrepancies/concerns that arise during the audit process.
    ix. Make photocopies for the auditor(s) if requested (always make a second copy for the site and maintain control of the site copies).
    x. Work with the study team to address and correct auditor observations.
    xi. Establish a planned date/time for the Exit Interview to be held when the audit/inspection has concluded. Ask the auditor/inspector who they would like to attend the exit interview. Provide assistance to the QA/Education Specialist by notifying each study team member and adding the information to the shared calendar. Ensure the PI is available for the Exit Interview.
    xii. Attend the Exit Interview at the conclusion of the audit/inspection, if possible.
d. CRC and/or DM
    i. Prior to the commencement of the audit/inspection, ensure all requested items are available for review in the designated auditing space or in the HIPAA compliance box folder set up for the audit, as applicable.
    ii. Review the layout of a subject chart with the auditor(s)/Inspector(s).
e. Regulatory Coordinator
    i. Unless specifically requested by the auditor(s)/Inspector(s), it is not necessary for the RC to be present during the audit/inspection.

f. Research Pharmacist
    i. Unless specifically requested by the auditor(s)/Inspector(s), it is not necessary for the Research Pharmacist to be present during the audit/inspection.
g. Exit Interview
    i. The following individuals will participate in the Exit Interview: PI, CTO AD, QA/Education Specialist, Asst. D-Regulatory, CTO Assoc. D, Lead CRC, Lead DM, Study RC, and Research Pharmacist (if applicable),
    ii. The Exit Interview will be held at the conclusion of the audit/inspection.
    iii. Audit/inspection findings are reviewed and discussed.
    iv. Every attempt should be made to resolve the auditor's/Inspector(s) concerns and queries prior to the close of the Exit Interview.
    v. The QA/Education Specialist will record the meeting minutes and provide a summary of key findings and action items to the study team, as described in the auditor's/Inspector(s) Exit Interview.
    vi. Within 24 hours, the QA/Education Specialist will communicate significant findings (e.g., issuance of a Form FDA 483, clinical hold, suspension, or other actionable finding) to the CTO AD, CTO MD, AD-CR, CTO Assoc. D, and Asst. D-Regulatory. The AD-CR will determine if findings should be forwarded to the PI's Department Chair.

5. Audit/Inspection Follow-Up

a. After the audit/inspection has been completed, the PI will receive a report or letter (in the case of the FDA) outlining the findings and issues that need to be addressed.
b. PI responsibilities are:
    i. Provide a copy of the audit report or letter to the QA/Education Specialist.
    ii. Work with the QA/Education Specialist to draft a preliminary response and corrective action and prevention plan (if necessary), refer to Attachment C within the timeframe specified on the audit/inspection report/letter. If no timeframe is provided, the preliminary response must be completed within 15 business days of receipt of the audit/inspection report.
c. QA/Education Specialist responsibilities are:
    i. Provide a copy of the audit/inspection report to the CTO AD, CTO MD, CTO Assoc. D, CTO Assist D-Regulatory, and the study team.
    ii. Work with the PI, appropriate members of the study team, the CTO AD (if the findings involve CTO processes or procedures), and, if the findings involve institutional policies, procedures or facilities (IRB policies, pharmacy procedures, etc.), appropriate institutional personnel, to draft a preliminary response and corrective action plan (if necessary) within the timeframe specified on the audit/inspection report. If no timeframe is provided, the preliminary response must be completed within 15 business days of receipt of the audit report. Once drafted, send a final draft for review to the CTO AD and CTO MD, prior to sending the final version to the appropriate recipient at the auditing agency.
    iii. Once approval is given, finalize the response.
    iv. Obtain PI and other necessary signatures on the final audit response.

v. Provide the audit/inspection response to the auditor(s) via the method specified in the audit/inspection report instructions, with a copy to the CTO AD, AD-CR, CTO Assoc. D, CTO Asst. D-Regulatory, the CTO MD, and the PI.
vi. For regulatory inspections, cooperative group audits, and for-cause audits, provide the audit report and response documents to the RC for submission to the IRB of record and the Data and Safety Monitoring Committee, when applicable.
vii. Distribute the final resolution from the auditing agency to the CTO AD, the CTO MD, AD-CR, CTO Assoc. D, CTO Asst. D-Regulatory and the PI. For regulatory inspections, cooperative group audits, and for-cause audits, provide the final audit resolution to the RC for submission to the IRB of record and the Data Safety Monitoring Committee, when applicable.
viii. Maintain all documentation associated with the audit/inspection including correspondence, meeting minutes, report of audit/inspection findings, and the audit/inspection response on K drive located in the study specific folder in the audit folder.

d. RC responsibilities are:
   i. Upon receipt of the audit/inspection report, the site's response, and the final audit resolution from the auditing entity from the QA/Education Specialist, submit them to the IRB as they are received as required, and file the IRB acknowledgement letters in the shared drive.
   ii. When applicable, submit these documents to the DSMC and file all correspondence in the shared drive.

REFERENCE(S) / RELATED POLICY(IES)

21 CFR 312.68 Inspection of investigator's records and reports

COLLABORATION

This policy was developed in collaboration with the following Departments:
University of Illinois Cancer Center, Clinical Trials Office (CTO)

ATTACHMENTS

A. Guidance on Hosting External Audits and Regulatory Agency Inspections
B. Guidance on Responding to Audit Findings
C. Example Template of a Corrective Action and Preventive Action Plan
D. Site FDA Inspection Preparation Checklist

ATTACHMENT A

University of Illinois Cancer Center | Clinical Trials Office

Guidance on Hosting External Audits and Regulatory Agency Inspections

Preparing for an External Audit or Regulatory Agency Inspection:
The most effective way to prepare for an external audit or regulatory inspection is to maintain the research documents in a compliant and thus "audit ready" condition at all times. Generally, external sponsors provide up to a month notice, but the Food and Drug Administration (FDA) or other regulatory agencies are only required to provide 24 hours of notice prior to the first day of the inspection.

Meeting and Greeting the Auditor or Inspector:
The PI should be available to meet and greet the auditor or inspector upon arrival.

For regulatory agency inspections:

- Greet the inspector. The PI or designee should also verify the inspector's credentials. **Do not** photocopy the inspector's credentials.
- Sign the Form FDA 482 (Notice of Intent to Audit) and retain a copy.

During the Audit/Inspection:

- The PI should adjust his/her schedule to be available to address questions or requests the auditor/inspector may have during the audit. The PI should plan on checking in with the auditor/inspector at the timeframes agreed upon with the auditor/inspector. Be sure to keep each appointment and do not make the auditor/inspector wait.
- The QA/Education Specialist will serve as a liaison to facilitate the auditor/inspector. This designated liaison will function as the auditor/inspector's escort. The escort will act as the coordinator for the audit and will keep written record of all audit related activities, including all document requests or requests for personnel interviews. Upon request, all research team members should be available to answer questions of **which they have direct knowledge.**
- Set the proper tone. Be available, maintain a professional, cordial, and cooperative demeanor at all times. Do not, under any circumstances, become defensive or argumentative.
- Provide the auditor/inspector with a comfortable place to work with ample space to organize materials. Keep the room free of non-protocol materials or subject information. Lock any cabinets and drawers in the room.

- Have medical records, research charts, and source documents available and provide only those specifically requested.
- Confirm with the auditor/inspector his/her preference for handling issues and queries. Remember to track all requests from the auditor/inspector and make photocopies, if appropriate.
- During the audit, it is likely the auditor/inspector will make "observations" relating to the conduct of the trial, documentation, etc. The QA/Education Specialist will work with the research team, making every effort to address and correct these observations while the audit/inspection is taking place.
- Do not volunteer information; answer all questions briefly, honestly, and accurately. Do not elaborate on a question unless questioned further for detail. When appropriate, limit responses to yes or no answers. Only answer questions of **which you have direct knowledge**. Be confident that your response is accurate and factual and be prepared to supply supporting documentation.
- If you are not sure how to answer a question or do not feel comfortable answering a question, it is appropriate to say, "I will get back to you". Then seek advice from the QA/Education Specialist, the CTO AD, or other appropriate personnel on how to address the question.
- Limit offers of hospitality to simple beverages such as water, coffee, tea, and juice. It is not appropriate to provide food items.
- Contact the sponsor or CRO with any questions or concerns, as appropriate.
- Institutional employees should not have discussions with the auditor/inspector in casual areas to discuss clinical operations or personnel. All conversations should occur in the presence of the QA/Education Specialist.
- The QA/Education Specialist will accompany the auditor/inspector at all times during the audit.

<u>The Exit Interview:</u>

- During the Exit Interview, tape recorders may not be used.
- Interactions during the Exit Interview should take place primarily between the PI and the auditor/inspector. Other members of the research team present should not attempt to contribute to the proceedings unless invited to do so.
- During the Exit Interview, politely identify for the auditor/inspector all observations addressed and/or corrected during the audit.
- If any observation noted deals with not meeting regulations, carefully point out that the regulations are subject to interpretation. Then explain your intentions and, if true, how your actions protected the subject(s).
- If you can clearly identify an appropriate corrective action in response to an observation, indicate what measures you plan to take to correct the observation immediately. **Do not** commit to a future action that you do not intend to make or are unable to fulfill.

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

ATTACHMENT B

University of Illinois Cancer Center | Clinical Trials Office

Guidance on Responding to Audit Findings

Formulating an Appropriate Response:

- Carefully review the audit/inspection report and ensure that you understand and are familiar with any deficiencies cited. Think critically about each violation and what circumstances led to its occurrence.
- For violations involving regulatory requirements or data management, it should be determined why the information is missing or discrepant and the information should be recovered and added when possible. The response to these types of violations should include information regarding how the violation was addressed and include a corrective action plan to ensure this type of violation will not be repeated in the future.
- If a violation involves failure to conduct protocol specific procedures (i.e., treatment administration, blood draws, recording vital signs, tissue sampling, drug accountability), investigate why the procedure was not completed and in addition to describing the circumstances that may have prevented protocol compliance, also provide a corrective and preventative action plan (CAPA) that will ensure systemic changes are implemented to prevent the problem from recurring.
- The response to audit/inspection findings is a formal communication and should be in memo or letter format.
    - Be clear and concise in the reply.
    - Use the audit/inspection report as an outline in formulating your response.
    - It is not acceptable to insert your response into the audit/inspection report.
    - Do not use shading or highlighting of any kind in your response to avoid text being obscured during photocopying.

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

ATTACHMENT C

Example of a Corrective and Prevention Action Plan

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

Example of a Corrective and Preventive Action (CAPA) Plan

CORRECTIVE AND PREVENTATIVE ACTION PLAN

Protocol:
CRC:
Principal Investigator:
Date of Report:

Section I

Identified Issue:

Evaluate the extent of the problem.

- *Document a brief description of the issue(s)*
- *How many subjects were impacted?*
- *Was any subject harmed or could have been harmed?*
- *Could this problem exist in other protocols that use the same processes and or procedures and staff?*

Section II

Causal Analysis:

What is the root cause?

- *Describe the reason the incident(s) occurred*
- *Investigate how and why the incident(s) occurred*
- *Is there multiple causes?*
- *Is it lack of trained staff?*
- *Is it processes and or procedures?*
- *Is it both?*

Section III

Corrective Action:

What are the resolutions?

- *Describe the corrective actions taken or planned*
- *Indicate who will perform the corrective actions and the timeframe for implementation*
- *Describe the processes and or procedures developed to prevent the problem in the future*

Section IV

Documentation of Staff Retraining (If Applicable):

Document the retraining of staff on the new processes and or procedures

Members Required to Attend Retraining
Attach Attendance Sheet with Minutes

Section V

Evaluation:

Describe follow-up and evaluation of the effectiveness of the new processes and or procedures

- *Document the timeframe for the evaluation*
- *Document who will be responsible for this evaluation*
- *Confirm that the new processes and or procedures have corrected the problem(s)*
- *Document that the problem(s) have been corrected*
- *Document the timeframe of re-reviewing our continued compliance of the processes and or procedures*

Event Reoccurrence:
Address reoccurrences and further preventative measures and retraining and process improvements

Section VI

Principal Investigator's Review of Corrective Action Plan and Acknowledgement of Continual Improvement:

I, Dr. <INSERT NAME> have read and agree with the CAPA plan and acknowledge my agreement to supervise and implement immediate corrective action to secure compliance.

_____ _____
Principal Investigator's Signature **Date of Review**

_____ _____
Corrective Action Plan Preparer's Signature **Date of Signature**

UNIVERSITY OF ILLINOIS CANCER CENTER
Bench to Community

ATTACHMENT D

Site FDA Inspection Preparation Checklist

SITE FDA INSPECTION PREPARATION CHECKLIST					
Task		**Items**	**Done**	**NA**	**Notes**
Audit Notification	Notify all parties of impending audit	Sponsor			
		IRB			
		Principal investigator			
		Subinvestigators			
		Pharmacy			
		Laborator(ies)			
		Medical Records			
		Administration			
		Legal counsel			
		Work space			
	Reserve audit space	phone			
		copier			
		table			
Organization	Study overview	Prepare general overview of study			
		List personnel and delegated responsibilities			
	Subject lists	List all subjects including name, contact info., enrollment and completion dates, and MRN#			
		List all subjects screened with enrollment or reason not enrolled			
File Management	Organize files by heading and arrange in chronological order	Protocol (all versions)			
		Investigators' Brochure (all versions)			
		Protocol amendments			
		Form FDA 1572 (all versions)			
		CVs (PI, subIs listed on 1572)			
	IRB files	Initial IRB approval letter			
		Initial IRB approved informed consent			
		Amendment approval letters			
		Approved amended informed consents			
		Signed original consent forms for enrolled subjects stapled to human subjects bill of rights			
		Signed original consent forms for screened subjects			
		Adverse experience submissions to IRB			
		IRB annual renewals			
	Communication	Sponsor correspondence			
		CRO correspondence			
		Monitoring Log			
	Laboratory	Laboratory certification(s)			
		Laboratory normal ranges			

		CV of laboratory director			
	Drug accountability	Records of drug reciept			
		Records of drug dispensing			
		Records of drug disposition or return			
	Adverse Events	Serious adverse event reports made to sponsor			
		Serious adverse event reports received from sponsor			
	Subject documents	Completed CRFs for each subject			
		Source documents/medical record for each subject			
Data Review	Collect and review data for all enrolled subjects	CRFs			
		Data correction forms for CRFs (where applicable)			
	Medical records and/or study files documenting data	Condition of all subjects enrolled at time of entry showing eligible			
		All exposure to test article			
		Concomitant medications			
		Clinical assessments of subject during study			
		Laboratory reports			
		Diagnostic test reports			
		Diagnostic test films (if applicable)			
		Dose modifications			
		Adverse events			
		Protocol exceptions			
		Early withdrawals			

Appendix 11: The University of Illinois System Policy on Financial Conflicts of Interest in Research

I. Policy Information

Policy Title: The University of Illinois System Policy on Financial Conflicts of Interest in Research
Policy Owner: Vice President for Academic Affairs
Responsible Official: Vice President for Academic Affairs (System); Vice Chancellor for Research (UIUC and UIC); Vice Chancellor for Academic Affairs (UIS)
Approved by: University of Illinois Board of Trustees
Date Approved: 07/19/2018
Effective Date: 07/19/2018
Targeted Review Date: 07/19/2023
Contact: System, coi@uillinois.edu; Chicago, coi@uic.edu; Springfield coi@uis.edu; Urbana-Champaign, coi@illinois.edu
Related Policies:

Policy on Conflicts of Commitment and Interest
Policy on Organizational Conflicts of Interest

II. Overview

This policy provides a framework for the University of Illinois System ("University") to comply with conflict of interest policies established by external sponsors of research. The procedures in sections V. A. and V. B. have different definitions, thresholds, and reporting requirements consistent with sponsor mandates. As standard procedure for any research supported by sponsors other than the organizations that have adopted the Public Health Services regulations, the University will apply the standards and procedures established under Section V. B. (National Science Foundation).

III. Scope

The Policy on Financial Conflicts of Interest in Research (FCOIR) applies to investigators and any other person responsible for the design, conduct or reporting of funded or human subjects research, including senior/key personnel identified in a grant application or progress or final report of research (each an "investigator"). The FCOIR Policy applies at the earlier of submission of a funding proposal or Institutional Review Board (IRB) application and remains applicable through the life of the funding award or study, whichever is longer.

IV. Statement of Policy

The University seeks to promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct, and reporting of research will be free from bias resulting from financial interests. The FCOIR Policy informs investigators about situations that generate financial conflicts of interest related to research and provides mechanisms for investigators and the University to eliminate or manage financial conflicts of interest that arise.

V. Procedures

A. Research supported by the Public Health Service (PHS) or organizations that adopted the PHS financial conflict of interest regulations

The Health and Human Services/PHS regulations on promoting objectivity in research apply to research projects supported by PHS agencies. Other non-federal entities may incorporate the PHS regulations in their award terms.

i. Definitions

Financial Conflict of Interest: A financial conflict of interest (FCOI) exists when the University of Illinois System, through its designated officials, reasonably determines that an investigator's significant financial interest (SFI) could directly and significantly affect the design, conduct, or reporting of the research.

Investigator: Investigator includes any person who is responsible for the design, conduct, or reporting of research, regardless of title or position.

Senior/Key Personnel: The Project Director or Principal Investigator and any other person identified as senior/key personnel by the University in the grant application, progress report, or any other report submitted to the PHS.

Significant Financial Interest: An SFI is defined at 42 C.F.R. § 50.603. SFI means a financial interest consisting of one or more of the following interests of the investigator (and spouse and dependent children) that reasonably appears related to the investigator's University responsibilities with regard to:

- a publicly traded entity if the value of any remuneration received from the entity as of the date of disclosure and in the 12 months preceding the disclosure exceeds $5,000, when aggregated. Remuneration includes salary, royalties, and other payments for services, such as consulting fees and honoraria paid authorship, equity interests, stock options or other ownership interests, as determined through public prices or reasonable measures of fair market value;
- a non-publicly traded entity, if the value of any remuneration received from the entity in the 12 months preceding the disclosure exceeds $5,000 when aggregated, or when the investigator holds any equity interest;
- intellectual property rights and interests (e.g. patents, copyrights) upon receipt of income related to such rights and interest; and
- reimbursed or sponsored travel related to investigator's University responsibilities if paid by a sponsor other than a federal, state, or local government agency, an institution of higher education as defined by 20 U.S.C. § 1001(a); an academic teaching hospital; a medical center; or a research institute affiliated with an institution of higher education.

The following financial interests are not considered to be an SFI:

- salary, royalties or other remunerations paid by the University of Illinois System to the investigator if the investigator is currently employed or appointed by the University, including intellectual property rights assigned to the University and agreements to share royalties related to such rights;
- income from investment vehicles (mutual funds or retirement account that are not managed directly by the individual);
- income from seminars, lectures, or teaching engagements sponsored by a federal, state, or local government agency, an institution of higher education as defined by 20 U.S.C. § 1001(a), an academic teaching hospital, a medical center, or a research institute that is affiliated with an institution of higher education; or
- income from service on advisory committees or review panels for a federal, state, or local government agency, an institution of higher education as defined by 20 U.S.C. § 1001(a)

(e.g., NIH review panel), an academic teaching hospital, a medical center, or a research institution that is affiliated with an institution of higher education.

ii. Disclosure

Investigators must disclose any SFI that reasonably appears to be related to the investigator's University responsibilities. Investigators must disclose SFIs annually and within 30 days of discovery or acquisition of a new or change in an SFI. Disclosures are made using the START myDisclosures on the sponsor specific questionnaire, https://myresearch.uillinois.edu/myDisclosures/.

iii. Review

Disclosed SFIs are reviewed by designated officials in each University's Conflict of Interest Office to assess if an SFI is reasonably related to a University research project. The reviewers take into account the nature and extent of an investigator's role on a project, the nature and extent of an investigator's SFIs, and the nature of the research activity under review. If the SFI is reasonably related, the reviewers will assess if the SFI could directly and significantly affect the design, conduct, or reporting of the research.

SFIs that have the potential to present a financial conflict of interest for a research project are referred to the applicable Unit Executive Officer for review and management. Management of FCOIs may include, but is not limited to, disclosure, impartial review, reduction or elimination of the investigator's role in certain aspects of the study, and additional monitoring.

Reviews and determinations must occur prior to expenditure of funds for new projects, within 60 days of newly disclosed SFIs, and within 60 days of the addition of new investigators to projects.

iv. Reporting

When the University determines that an SFI is related to sponsored research, the Responsible Official or their delegate (e.g., the Vice Chancellor for Research or equivalent office) must submit reports as required by the sponsor. The Responsible Official must submit the FCOI Report:

- prior to the expenditure of funds;
- within 60 days of identification for an investigator who is newly participating in the project;
- within 60 days for new, or newly identified, FCOIs for existing investigators.

After the FCOI Report is initiated, the Responsible Official or their delegate must provide to the sponsor status updates and identify changes in management plans, at least annually, until the completion of the project.

v. Noncompliance

The following are examples of noncompliance with the FCOIR Policy:

a) failure to submit a timely disclosure;
b) submission of an incomplete, erroneous or misleading initial, updated or annual disclosure;
c) failure to disclose information as required by the FCOIR Policy; and

d) failure to comply with prescribed management plans.

When noncompliance is identified, the Responsible Official or their delegate will implement a management plan within 60 days.

In addition, the OVCR or equivalent office must conduct a retrospective review of the investigator's research activities on the project to determine if there is bias in the design, conduct, or reporting of the research resulting from the financial conflict of interest. The retrospective review must be completed within 120 days of the determination of noncompliance. If bias is found in the course of the retrospective review, the OVCR or equivalent office must promptly notify the sponsor and submit a mitigation report that addresses the impact of the bias on the research and the university's plan of action to eliminate or mitigate the effect of the bias.

If non-compliance is identified related to a clinical research project whose purpose is to evaluate the safety or effectiveness of a drug, medical device, or treatment, the investigator is required to:

1) disclose the FCOI in each public presentation of the results of the research; and
2) request an addendum to previously published presentations.

vi. Training

Each investigator on an award supported by the PHS must complete University-approved conflicts of interest training prior to engaging in PHS-funded research and thereafter every four years unless immediate retraining is required for any of the following circumstances:

- the University revises the FCOIR Policy and procedures in any manner that affects the requirements of the investigator;
- an investigator is new to the University;
- the University finds that an investigator is not in compliance with the FCOIR Policy or with an approved management plan.

Training is developed and overseen by the Office of Vice Chancellor for Research and administered through the START myDisclosures application.

vii. Subrecipient Compliance

If the University carries out the research through use of a subrecipient or subcontractor ("subrecipient"), the University must require the subrecipient to comply with either the University's FCOIR Policy or the subrecipient's financial conflicts of interest policy. If the latter, then the subrecipient must certify that its policy complies with the PHS regulations. The subrecipient agreement must specify deadlines for the subrecipient to submit all SFI disclosures or reports of conflicts to the University so that the University can meet its own reporting obligations.

viii. Public Access to Information

Upon written request, the University must make available to the public within five business days certain information about the SFIs held by senior/key personnel that constitute a FCOI related to the research. The minimal information to be provided is

described at 42 C.F.R. § 50.605(a)(5)(ii). The Responsible Official or their delegate will coordinate requests and responses.

B. Research sponsored by the National Science Foundation (NSF) or an organization that has adopted the NSF's conflict of interest policy

i. Definitions

Conflict of Interest: A COI exists when the University, through its designated officials, reasonably determines that an investigator's SFI could directly and significantly affect the design, conduct, or reporting of the NSF-funded activities.

Investigator: The principal investigator, co-principal investigators/co-project directors, and any other person at the University who is responsible for the design, conduct, or reporting of research or educational activities funded or proposed for funding.

Significant Financial Interest: An SFI means anything of monetary value, including, but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interest (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights).

SFI does not include:

- salary, royalties or other remuneration from the University;
- income from seminars, lectures, or teaching engagements sponsored by public or non-profit entities;
- income from service on advisory committees or review panels for public or non-profit entities;
- an equity interest that, when aggregated for the investigator and the investigator's spouse and dependent children, meets both of the following tests: does not exceed $5,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than 5% ownership interest in any single entity; or
- salary, royalties or other payments that, when aggregated for the investigator and the investigator's spouse or dependent children, are not expected to exceed $5,000 during the prior 12-month period.

ii. Disclosure

Investigators must disclose any SFI at the time the proposal is submitted to NSF. Investigators must disclose SFIs annually and within 30 days of discovery or acquisition of a new or change in a SFI. Disclosures are made on the RNUA. If the interest is related to a sponsored research project, the investigator will also complete the sponsor specific questionnaire. Disclosures are submitted through START myDisclosures: https://myresearch.uillinois.edu/myDisclosures/

iii. Review

SFIs are reviewed by designated officials in each University's Conflict of Interest Office to assess if the SFI is reasonably related to an NSF-funded research project. The reviewers

take into account the nature and extent of an investigator's role on a project, the nature and extent of an investigator's SFIs, and the nature of the research activity under review. If the SFI could be reasonably related, the reviewers will assess if the SFI could directly and significantly affect the design, conduct, or reporting of research.

SFIs that present a COI are referred to the applicable Unit Executive Officer for review and elimination or management. Management of FCOI may include, but is not limited to, disclosure, impartial review, reduction or elimination of the investigator's role in certain aspects of the study, and/or additional monitoring. COIs must be managed, reduced, or eliminated prior to the expenditure of the award funds.

If the reviewers determine that imposing conditions or restrictions would be either ineffective or inequitable, and that the potential negative impacts that may arise from a SFI are outweighed by interests of scientific progress, technology transfer, or the public health and welfare, then the Vice Chancellor for Research or equivalent office may allow the research to go forward without imposing such conditions or restrictions.

iv. Reporting

The University must inform the NSF Office of the General Counsel if the University finds that it is unable to satisfactorily manage a COI and if it finds that the research will proceed without the imposition of conditions or restrictions when a conflict of interest exists.

v. Subrecipient Compliance

If the University carries out NSF-funded research through subrecipients, contractors, or collaborators (each a "subrecipient"), the University must take reasonable steps to ensure that either: the subrecipient has its own policies in place that meet the requirements of the NSF; or the investigators working for the subrecipient will follow the University's policies.

C. Clinical Studies Supporting Food and Drug Administration (FDA) Applications

Applicants who submit a marketing application to the FDA for a new drug, biological product, or medical device must include financial disclosures of any clinical investigator directly involved in the conduct of clinical studies covered by 21 C.F.R. part 54 (each a "covered clinical study"). The FDA wants to review the financial interests and arrangements of clinical investigators in cases where they could bias the clinical studies used to support marketing applications. The sponsor of a covered clinical study must obtain financial disclosures from clinical investigators before allowing them to participate in any such study. Because the definition of sponsor is broad under this regulation, the University would be a sponsor if it provides study funding or if one or more of its employees designs and conducts a covered clinical study, regardless of the funding source. There may be multiple sponsors of a covered clinical study. Where the clinical investigator is not an employee of the sponsor, the investigator must cooperate with the sponsor and provide sufficient accurate information to allow for complete disclosure.

VI. Administrative Action and Sanctions

Failure by an investigator to comply with the requirements for conflicts training, financial disclosure, and management of conflicts may result in sanctions and administrative actions. Administrative actions may

include delay in award execution or suspension of the research project. Sanctions, when necessary, will be consistent with the University *Policy on Conflicts of Commitment and Interest*.

VII. Confidentiality

Access to information collected in connection with the FCOIR Policy will be limited to those with a need to know and will be shared in accordance with the requirements of law and University policies.

VIII. Record Retention

Financial disclosures and management plans must be maintained by the University for the longer of three years after termination or completion of the award or the period prescribed by the sponsor or applicable law.

IX. Sponsor oversight

The University will comply with all reasonable requests for additional information or oversight by the sponsor agency.

X. Related Laws, Guidance, and Policies

HHS/PHS Regulations: *Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought and Responsible Prospective Contractors*, 42 C.F.R. part 50 and 45 C.F.R. part 94. Final Rule at 76 Fed. Reg. 53256 (Aug. 25, 2011).
https://www.federalregister.gov/documents/2011/08/25/2011-21633/responsibility-of-applicants-for-promoting-objectivity-in-research-for-which-public-health-service

NSF Policy: Proposal and Award Policies and Procedures Guide, effective Jan. 30, 2017.
https://www.nsf.gov/publications/pub_summ.jsp?ods_key=gpg

FDA Regulations: Financial Disclosure by Clinical Investigators, 21 C.F.R. part 54.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=54

Association for the Accreditation of Human Research Protection Programs (AAHRPP), Standard 1-6,
http://www.aahrpp.org/apply/web-document-library/domain-i-organization

State of Illinois Freedom of Information Act, 5 ILCS 140.
https://www.uillinois.edu/foia