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1 INTRODUCTION

The Yale Cancer Center (YCC) is committed to ensuring the safety of patients participating in clinical trials and requires all clinical trials conducted at the YCC to include provisions for data and safety monitoring. The development of protocol monitoring plans and reporting requirements are dependent upon the overall risk to patients, the nature of the intervention, the phase of the trial and prior safety data with the proposed intervention, the role of the Yale principal investigator and the institution, and the role of the study sponsor. In addition, the plan must be integrated into the overall structure of clinical trial data and safety monitoring covered by other policies within the Yale School of Medicine.

2 MONITORING THE PROGRESS OF TRIALS AND THE SAFETY OF PARTICIPANTS

2.1 OVERVIEW

The YCC Data and Safety Monitoring Plan (DSMP) recognizes three essential components of responsibility:

- Principal Investigator’s responsibility for continually reviewing the conduct of the study, the prompt assessment and reporting of adverse events, and requirements for compliance with Federal regulations, University policies, and sponsor requirements.
- YCC oversight committee review of audit reports, safety and other study data.
- YCC and/ or study sponsor audits and monitoring of source records and study data to assure compliance with the protocol, appropriate conduct of the study, compliance with federal and institutional regulations, prompt and complete reporting of unanticipated problems to appropriate oversight groups, and accuracy of the database.

While the YCC Director holds the primary responsibility for Yale Cancer Center data and safety monitoring, the Principal Investigator (PI) and other individuals, along with the Disease-Aligned Research Teams (DARTs), have responsibilities for data and safety monitoring. As the specific types of monitoring and reporting vary by the nature of the individual trial, the responsibilities to ensure that the monitoring is timely and effective include several YCC committees and offices including:

- YCC Clinical Research Oversight Committee (CROC)
- YCC Disease-Aligned Research Teams (DARTs)
- YCC Protocol Review Committee (PRC)
- YCC Protocol Life Cycle Subcommittee (PLCS)
- YCC Data and Safety Monitoring Committee (DSMC)
- YCC Clinical Trials Office (CTO)
- Office of Quality Assurance and Training
- Yale Human Research Protection Program
- Yale Center for Clinical Investigation (YCCI) Multicenter Unit
- Conflict of Interest Office
2.2 Institutional Oversight of Clinical Trials

2.2.1 Overview of Clinical Research Process

2.2.2 Clinical Research Oversight Committee (CROC)

The Clinical Research Oversight Committee is comprised of Yale Cancer Center leadership and Smilow Cancer Hospital (SCH) leadership together with several DART leaders. The committee reviews clinical research issues, DART portfolios, and CTO operations. CROC is consulted for policy issues involving DART usage, investigator conduct, and resource allocation. CROC meets bimonthly.

2.2.3 Disease-Aligned Research Team (DART)

The Disease-Aligned Research Teams (DARTs) at Yale Cancer Center promote translational research at Smilow Cancer Hospital through scientific discovery, testing new discoveries in clinics and, ultimately, turning new innovations into viable disease-specific therapeutics. The Yale Cancer Center DART leaders and Research
Program leaders collaborate to ensure all research opportunities are well coordinated and cooperative translational research is a priority for all Yale Cancer Center members.

The DART is led by a senior member of the Yale Cancer Center and supported by a DART specific clinical research team comprised of investigators (i.e., MDs, DOs and Advanced Practice Providers), Clinical Trial Team Manager (CTTM), and other research support staff such as Clinical Research Coordinators, Clinical Research Assistants and Regulatory Assistants, who assist the DART leader in the review and submission process. Proposed protocols are initially discussed by the DART, including disease-oriented and modality DARTs (e.g., Phase 1 and Therapeutic Radiology). Then, upon the subsequent approval of the DART leader, proposed protocols are submitted by the research team to the Protocol Review and Monitoring System (PRMS) for review by the PRC. Goals of the DART review process are to assess for scientific merit, portfolio suitability, feasibility, and consistency with overall YCC goals.

Each DART meets on a regular basis, typically once a week.

2.2.4 Protocol Review Committee (PRC)

The Protocol Review Committee was established in the early 1990’s and conducts a review of all cancer-related therapeutic and non-therapeutic clinical trials conducted at the Yale Cancer Center, based on specific criteria, prior to approval and study initiation. The Yale University Human Research Protection Program (HRPP) requires PRC approval be obtained prior to IRB approval.

Objectives:
- To evaluate the scientific rationale for the protocol.
• To assure that the patient population is appropriate; that the risk/benefit ratio is appropriate; and that the study provides maximum protection for patient safety.
• To assess the adequacy of the endpoints, and to determine that high quality and appropriate background clinical trial and statistical design have been incorporated into the protocol.
• To prioritize the protocol, based on scientific merit, and with consideration of other protocols available within the institution.
• To assure the protocol will be conducted according to applicable institutional and Federal regulations, and the relevant lead investigators have the experience and training to conduct the trial safely and in compliance with all regulations.

The PRC is comprised of voting and non-voting members. The YCC Director appoints all members of the PRC and the PRC Chair(s). There will be a minimum of ten voting members of the PRC. Membership includes a broad range of representation from the YCC investigational community and consists largely of those who are engaged daily in clinical research activities, protocol oversight, design and conduct. For studies requiring special expertise, the PRC Chair may request the YCC Director appoint ad hoc non-voting members to provide advice on protocols.

The voting members of the PRC will represent the following disciplines:

- Basic Laboratory
- Prevention
- Clinical
- Cancer Control
- Population-Based Science
- Radiation
- Surgery
- Biostatistics

The PRC meets twice a month. The review process is initiated by the submission of the required protocol information to the PRC by the Principal Investigator. The protocol must receive at least conditional approval by the PRC, prior to review by the Yale IRB. Cancer Center studies cannot be activated until both the IRB and PRC provide approval.

2.2.5 Protocol Life Cycle Subcommittee of the PRC (PLCS)

The Protocol Life Cycle Subcommittee of the PRC meets monthly to peer review DART portfolios and protocol accruals. The sub-committee is comprised of senior members of the PRC. Each DART presents semiannually. Protocol accrual across all the DARTs are reviewed each meeting using a report generated from the Clinical Trials Management System (OnCore) showing the monthly accrual.

2.2.6 Data and Safety Monitoring Committee (DSMC)

The purpose of the Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) is to provide ongoing data and safety monitoring for all interventional cancer clinical trials, which include therapeutic, interventional prevention and interventional supportive care studies. The Committee reviews all serious unanticipated problems (SAEs), protocol-level and subject-level deviations, and internal and external audit reports on a monthly basis and protocol specific data and safety monitoring reports at the frequency initially determined by the Protocol Review Committee based on trial sponsorship and risk. For example, interventional
Yale Cancer Center Investigator-Initiated Trials (IITs) are reviewed a minimum of every six months. The DSMC has authority to intervene in the conduct of these studies as necessary to ensure the safety of the participants and to maintain the highest quality in the clinical research performed at YCC.

The YCC DSMC is an oversight committee, which is an integral component to both the YCC institutional Data and Safety Monitoring Plan and protocol specific data and safety monitoring for trials conducted at YCC. The DSMC is comprised of both voting and non-voting members. The YCC Director appoints all members of the DSMC and the DSMC Chair. There will be a minimum of ten voting members of the DSMC. A minimum of six voting members must be present to satisfy quorum for a meeting. Voting members may include physicians, statisticians, and nurses, based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of clinical trial methodology. For studies requiring special expertise, the YCC Chair may request the YCC Director appoint ad hoc non-voting members to provide advice on protocols.

The voting members of the DSMC will represent the following disciplines:
- Medical Oncology
- Radiation Oncology
- Surgery
- Yale IRB
- Biostatistics

Meetings are held monthly and on an ad hoc basis. The meeting structure includes the review and approval of past minutes, follow-up on past identified action items, presentation and discussion of internal and external audits, review and discussion of the monthly SAE report, review and discussion of the monthly deviation report and review, discussion and determinations of the protocol specific DSMC reviews.

2.2.7 Human Research Protection Program (HRPP)

Under the oversight of the Deputy Provost for Research, the Yale Human Research Protection Program (HRPP) is responsible for the protection of the rights and welfare of human subjects in research projects conducted at Yale, by Yale faculty, staff and students, and by investigators from several affiliate institutions. The program provides IRB oversight, administrative support, and educational training for investigators and research staff to ensure that Yale research complies with Federal and State regulations, University policy, and the highest ethical standards.

The Yale HRPP provides administrative and regulatory support for four biomedical Institutional Review Boards (IRB), known locally as Human Investigation Committee (HIC) IA, IB, II, III and IV, and for one social, behavioral and educational IRB, known locally as the Human Subjects Committee (HSC). Yale HRPP has oversight over clinical trials conducted by YCC and may approve the use of an external IRB to serve as the IRB of record such as the NCI Central IRBs (CIRB) or other external IRBs with whom Yale HRPP has entered into an IRB Authorization Agreement. If the use of an external IRB is not approved by Yale HRPP or not requested by the PI, clinical trials conducted by YCC will be reviewed and overseen by the on-site HICs or HSC, as appropriate.

2.2.8 Institutional Review Boards (IRBs)

2.2.8.1 Yale IRBs
Yale IRBs have Federalwide Assurance (FWA) with the United States Department of Health and Human Services (DHHS). In addition to the terms of the FWA, Yale IRBs comply with all applicable regulations and policies set forth in 21 CFR Parts 50 and 56 of the DHHS Food and Drug Administration. Yale IRBs reviewing FDA-regulated studies are registered as such with the Office for Human Research Protections (OHRP). Yale HRPP has maintained full accreditation from the Association for Accreditation of Human Research Protection Programs (AAHRPP) since December 2010. To ensure the ethical conduct of research involving human participants, Yale requires that all individuals engaged in research be under the purview of a federally registered IRB.

Yale IRBs comply with the written policies and procedures of the Yale HRPP for the protection of human subjects.

Membership requires careful review of research protocols with emphasis on human subject protections issues, to ensure that research design is sound and study hypothesis is reasonable, risks to subjects are minimized, risks to subjects are reasonable in relation to anticipated benefits, selection of subjects is equitable, informed consent is obtained or appropriately waived from all prospective subjects and documented, the research protocol includes a plan for data and safety monitoring, subject’s privacy and confidentiality are protected and appropriate additional safeguards are incorporated for any vulnerable subjects. Each member brings a different voice and set of life experiences to the discussion. Members represent the various academic disciplines whose research is reviewed by the Committee as well as at least one member who is not affiliated with Yale.

2.2.8.2 External IRBs

Yale HRPP may authorize use of an external IRB for review of certain types of research studies. The external IRB shall be Yale University’s IRB of record and will perform IRB functions in compliance with applicable laws, regulations, guidance, contractual obligations, and Yale University policy for the life of the study subject to the right of Yale University to withdraw a study from ceded review.

2.2.9 Office of Quality Assurance and Training

The Office of Quality Assurance and Training (formerly known as the Office of Protocol Review and Monitoring) was established in 2005 and is the coordinating office for YCC’s PRC, PLCS, and DSMC, the internal audit program and the broad training program for clinical trial staff. The Office of Quality Assurance and Training maintains the records of all committee meeting agendas, minutes and correspondence related to these activities. Training records are maintained in the office and tracked in the University’s Training Management System.

2.2.10 YCC Clinical Trials Office (CTO)

The Yale Cancer Center (YCC) Clinical Trials Office (CTO), the Clinical Protocol and Data Management (CPDM) component, is the central management and operations organization for all clinical trials at YCC. Its primary goals are: 1) to facilitate efficient activation and conduct of therapeutic interventional trials in cancer across all disciplines at Yale Cancer Center; and 2) to provide optimal infrastructure for the conduct of such trials, oversight of personnel through highest-level SOPs that ensure accurate conduct of protocol-mandated procedures and data capture, and full regulatory compliance with all trial aspects.
2.2.11 Yale Center for Clinical Investigation (YCCI) Multi-Center Unit

In 2014, Yale University established centralized support for investigator-initiated multi-center trials. A Multi-Center Unit (MCU) was established in collaboration between Yale Center for Clinical Investigation (YCCI, Yale University’s Clinical and Translational Science Aware (CTSA)) and YCC. This office provides necessary support and oversight for all external collaborating sites, including sponsor-level project management, investigational new drug (IND) application submission and maintenance, regulatory support, document management (bi-directionally), and data monitoring.

2.3 Prior to Protocol Activation

2.3.1 Disease-Aligned Research Team (DART) Review

Each of the Disease-Aligned Research Teams (DART), which are teams aligned based on disease and/ or modality, conduct an internal review addressing protocol development, appropriate use of resources, scientific merit, development of IITs, and state-of-the-art clinical trial conduct, yielding robust accrual. All elements are documented on the DART Protocol Review Form which upon DART approval is submitted with the required protocol documents to PRC.

The DART Leader is expected to responsibly assess protocol proposals for use of resources, merit, priority, and congruence with YCC goals from the team’s perspective and share these insights with the PRC. This process is reflected in the DART Protocol Review Form that is submitted with each protocol and signed by the PI and the DART leader.

2.3.2 Protocol Review Committee (PRC) Review

Protocol Review Committee review requirements by protocol type are outlined in Appendix I. The following protocols must be reviewed by the PRC:

- Interventions for the treatment, staging or diagnosis of cancer or cancer-related problems
- Interventions to obtain specimens from cancer patients for the sole purpose of performing basic laboratory studies related to cancer
- Interventions to obtain specimens from normal subjects for the sole purpose of performing basic laboratory research studies related to cancer
- Use of stored specimens from cancer patients or normal subjects for basic laboratory research related to cancer
- Interventions for the prevention of cancer
- Interventions for the determination, management and study of cancer risk in normal subjects
- Interventions for the detection of cancer in normal subjects

All therapeutic and non-therapeutic studies requiring an intervention are reviewed by the PRC at a convened meeting. Non-therapeutic studies, such as quality of life studies, are administratively reviewed by the Office of Quality Assurance and Training and acknowledged at the next convened full committee meeting. National Clinical Trials Network (NCTN) and federally funded trials subject to external peer review are reviewed in an expedited fashion by the Chair or co-Chairs and are acknowledged by the PRC at the next convened full committee meeting. Non-hypothesis driven research is exempt from PRC review.

The Protocol Review Committee (PRC) is responsible for the initial assignment of a protocol specific Data and Safety Monitoring Plan. At the time of the initial review, the PRC evaluates the study to determine an adequate
protocol specific Data and Safety Monitoring Plan in the context of the risk level of the study, the existence of a plan for external monitoring by the sponsor or an independent Data and Safety Monitoring Board (DSMB) and other special circumstances that the committee feels will impact the safety of the participants. In IITs, data safety monitoring plans are required within the text of the protocol, indicating the investigator’s plan for monitoring. Typically for studies without external monitoring, such as IITs, the institutional Data and Safety Monitoring Plan includes DSMC review every six months. Based upon their review and evaluation, the PRC may assign higher risk studies, regardless of external monitoring, six month or more frequent reviews by the YCC DSMC.

The PRC will be provided the risk assessment score sheet, completed by the Office of Quality Assurance and Training, for every trial reviewed. The risk assessment total score guides the timing of the initial internal audit; however, the PRC may adjust the initial audit trigger based on their review. In addition to the internal data and safety monitoring plan which includes the risk based internal audit trigger, the requirement for submitting safety and response data to the YCC DSMC will be determined by the PRC.

NCTN and other federally funded studies are submitted to the PRC but do not undergo the same full committee review that is required for industry and investigator-initiated studies, as these are already peer reviewed. The risk assessment is conducted by the Office of Quality Assurance and Training and the data and safety monitoring plan is reviewed and approved by the committee chair, vice-chair, or designee at time of review. These submissions are approved by the chair, vice-chair, or designee via expedited review and their approval is listed in the PRC agenda for notification to PRC membership at the next convened meeting.

Non-Therapeutic studies are reviewed administratively and acknowledged by the Office of Quality Assurance and Training. The risk assessment is conducted by the Office of Quality Assurance and Training and the data and safety monitoring plan is assigned and recorded in OnCore. These submissions are listed in the PRC agenda for notification to PRC membership at the next convened meeting.

The YCC PRC Charter specifies the operational processes for all review types, including full committee review, expedited chair review and administrative review.

2.3.3 *Clinical Research Oversight Committee (CROC)*

YCC Multicenter IITs require additional review by CROC to ensure that appropriate resources are available to conduct the study.

2.3.4 *Institutional Review Board (IRB) Review*

The Yale IRBs or an external IRB approved by Yale HRPP as the IRB of record review all research involving human subjects conducted by the YCC. The IRB may approve, require clarifications or modifications, or disapprove research. IRB initial approval must be obtained before conducting any human subjects research. The YCC, in collaboration with the Yale Human Research Protections Program (HRPP), which oversees all Yale IRBs and use of external IRBs, have put into place a system of checks and balances to ensure all cancer-related protocols are reviewed by the PRC prior to IRB review.

2.4 **Post Activation and Ongoing Monitoring**

2.4.1 *Disease-Aligned Research Team (DART)*
2.4.1.1 Overview

Each DART has the responsibility to ensure that the following data and safety procedures are conducted in accordance with YCC and institutional policies after a research protocol has been activated and opened to accrual.

2.4.1.2 DART Responsibilities for DSMC Review

Data and Safety Monitoring Reports
The Principal Investigator or research team designee will prepare a Data and Safety Monitoring Report for each protocol being monitored by the DSMC. This report will summarize the status of the study, including enrollment and toxicity information, and may also contain recommendations regarding study related issues for consideration by the DSMC. The report will follow a template distributed by Office of Quality Assurance and Training staff to the research teams.

External Audit Reports
The Principal Investigator or research team designee is required to submit external audit reports upon receipt, not interim monitoring reports, to the DSMC for review. This includes National Clinical Trials Network (NCTN) audit reports, industry sponsor-led for cause, routine and Good Clinical Practice (GCP) audit reports and FDA Form 483s and other written observations issued by FDA.

2.4.1.3 DART Responsibilities for PRMS Review

The PRMS assesses overall accrual and slow-accruing protocols every month at the PLCS meeting. The DART leader presents the team research portfolio including prioritizing of studies within the same patient population and accrual tables for peer review and discussion every six months.

2.4.2 Protocol Review Committee (PRC)

Substantial changes to protocols including changes to the drug type, dosing, or schedule; methods of response evaluation; study objectives (primary and secondary); and the statistics or statistical analysis plan must be submitted to the PRC prior to submission to the IRB. Amendments will be initially reviewed by the Chair or Vice-Chair of the PRC. Changes to the protocol can be approved by one of the Chairs or committee designee. The amendment reviewer may designate an amendment for review to the PRC committee for full review at a convened meeting. The PRC may require a change to the DSMP based on the amendment, which would be communicated to the PI and research team via PRC approval letter.

2.4.3 Protocol Life Cycle Subcommittee

Scientific progress and accrual progress is reviewed at the PLCS in conjunction with complete assessment of the disease team. DART leaders present their clinical trial portfolios in person, including all active and pending studies, targeted accrual, and actual accrual to date, as well as the rationale for and status of each study. Protocols that are open to enrollment and protocols with subjects actively receiving the study intervention are reviewed for continuing validity of the scientific question as well as the anticipated timeframe for completion. The PLCS will evaluate the scientific progress of all interventional trials that are open to enrollment at the time of the
DART portfolio review. Trials that are no longer scientifically relevant or will not meet their scientific objective will be discussed. If the committee does not feel that the PI’s attestation to scientific relevance is adequate, the trial will be recommended to the PRC for closure to further accrual.

The PLCS functions under accrual monitoring guidelines adopted in March 2017 requiring automatic closures using the milestones as described in the YCC Accrual Monitoring Policy. The following accrual monitoring rules will be used for all interventional clinical trials that are open to enrollment, except for trials of rare diseases (incidence of ≤ 6/100,000 per year).

<table>
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<th>Assessment Time</th>
<th>Percentage of Target Accrual Rate</th>
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<td>3 months</td>
<td>0%</td>
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<td>Closure</td>
</tr>
<tr>
<td>9 months</td>
<td>&lt; 30%</td>
<td>Warning</td>
</tr>
<tr>
<td>12 months</td>
<td>&lt;30%</td>
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<td>15 months</td>
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<td>21 months</td>
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<td>Warning</td>
</tr>
<tr>
<td>24 months</td>
<td>&lt;50%</td>
<td>Closure</td>
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The PLCS will reference the following guidance during discussion of trials of rare diseases (incidence of ≤ 6/100,000 per year) that are active at the time of DART review. Screening activities will be considered for these purposes. A separate accrual monitoring report from OnCore is used to assess trials of rare diseases in the DART portfolio.
PLCS reviews these closures for extenuating circumstances and forwards to PRC for closure. PIs may appeal such decisions to the PRC. Appeals regarding decisions from the Protocol Life-Cycle Subcommittee (PLCS) and Protocol Review Committee (PRC) will be submitted to the Clinical Research Oversight Committee (CROC) for initial review. The CROC review and recommendation on the appeal will be submitted to the PRC for their decision on the appeal. The PRC has final and absolute authority on all appeals related to the PRMS. The PRC has the authority to close any study.

### 2.4.4 Institutional Review Board (IRB)

#### 2.4.4.1 Yale IRBs

The IRB will review modifications, continuing reviews, reportable new information and closure requests post-initial approval.

**Modifications:** Any change to the IRB-approved protocol and/or study plan must be prospectively reviewed and approved by the IRB before implementation. The IRB will ultimately determine when re-consenting is appropriate and notify the PI as such in the IRB approval letter. Modification submissions will include revised study documents such as the protocol, consent form, investigator’s brochure and/or patient facing materials and a comprehensive summary of changes which includes a re-consenting plan proposed by the PI.

**Continuing Reviews:** Continuing review is conducted at least annually for all studies except qualifying minimal risk studies. Continuing review submissions will include information pertaining to local and study-wide enrollment totals, research milestones, new conflicts of interest, study progress to date, unanticipated problems and unexpected harm, adverse events, subject withdrawal, complaints, publications, interim findings, data and safety monitoring reports, regulatory action or other relevant information especially pertaining to safety and risk, and the risk to benefit ratio.
Reportable New Information: PIs are responsible for promptly reporting deviations and incidents of noncompliance which are deemed potentially serious and/or continuing to the IRB along with any proposed corrective and preventive action plan to ensure the safety of research participants and others and future compliance with the approved protocol and to prevent reoccurrence. The IRB or qualified designee will promptly review and/or investigate reports of deviations and/or noncompliance and take appropriate actions.

PIs are responsible for promptly reporting unanticipated problems involving risks to subjects or other to the IRB which are deemed unexpected, related or possibly related and harmful. The IRB Chair or convened IRBs are responsible for making the final determination that a reported event is a UPIRSO.

PIs are also responsible for promptly reporting new or increased risk information, adverse events or investigational new drug safety reports which require a change to the protocol or consent document(s), unanticipated adverse device effects, multiple occurrences of an unanticipated problem based upon aggregate analysis, audit or inspection findings, state medical board action, written reports from federal regulatory agencies, data and safety monitoring reports, researcher error, protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject, breaches of privacy and/or confidentiality and data security, subject or other complaints that cannot be resolved by the study team, holds, suspensions or termination of the research, incarceration of a subject in a study not approved to enroll prisoners and other information that the PI wishes to report that does otherwise not meet the criteria for prompt reporting.

A breach of privacy and/or confidentiality and data security issues are assessed by the Yale University Health Insurance Portability and Accountability Act (HIPAA) Privacy Officer in consultation with the Office of the General Counsel and, when appropriate, with Information Technology Services. PIs are responsible for reporting mishandling of protected health information to the Yale HIPAA Privacy Office for tracking and review. If the Privacy Officer determines that a breach has occurred, the affected subject(s) and Department of Health and Human Services will be notified in the time and manner required by law. The media will be notified, as required by law. Any incident that constitutes a breach is promptly reportable to the IRB.

The IRB has the authority to take whatever action it deems appropriate, up to and including suspension or termination of the research that is not being conducted in accordance with IRB policies, state law, and federal law, or that involves allegations of misconduct, or has been associated with an unanticipated problem involving risks to subjects or others or that has been associated with unexpected serious harm to subjects or others. Except in cases of imminent harm to research participants or others, the IRB will not suspend approval of research studies until the investigator has had an opportunity to respond to the initial allegation(s) of noncompliance.

Closure
A protocol can be closed with the IRB when the study is permanently closed to enrollment (or enrollment never started), all research-related interventions or interactions with human subjects have been completed, and all data collection and analysis of identifiable private information have been completed.
2.4.4.2 CIRB and Other External IRBs

The CIRB and other external IRBs will review modifications, continuing reviews, reportable new information and closure requests post-initial approval. Submissions are made according to the written policies and procedures of the IRB of record.

2.4.5 Data and Safety Monitoring Committee (DSMC)

The DSMC reviews all SAEs, protocol-level and subject-level deviations, and internal and external audit reports monthly and protocol specific data and safety monitoring reports per designated review timeframes. For trials that have zero accrual at their scheduled DSMC review, the DSMC will acknowledge the trials by placing them on a dedicated section of the agenda and by scheduling a future review, however no protocol specific determination will be made as no review of subject safety, deviations or data can take place.

2.4.5.1 Data and Safety Monitoring Reports (DSMR)

Data and Safety Monitoring Reports, using a standardized reporting format, are required to be submitted based on the schedule determined by the initial PRC review and include:

- Objectives of the study
- Design and treatment administration
- Safety data including PI’s observation of expectedness and unexpectedness of observed toxicities
- Dose Limiting Toxicities for Phase 1 studies
- Summary of efficacy results
- Study specific stopping rules with PI comments on status
- Conclusion and Plans
- Electronic case report form (eCRF) completeness - No more than 10% of the eCRF data should be outstanding at any given time while the trial is active.

Additionally, a review of the existing trial data in OnCore is conducted, including review of the following:

- Total number of subjects entered on each trial
- Total number of subjects treated
- Safety data by subject, dose levels administered, arms of study, and agent(s) involved
- A summary of all adverse events reported to date using CTC grading criteria as defined in the protocol
- A specific list of adverse events requiring expedited reporting – to include ALL serious adverse events (SAE’s)

The DSMC also conducts additional reviews for Yale Investigator-Initiated Multi-center trials. Subject enrollment, SAE, deviation, and eCRF completion data are broken down by each participating site for review.

The DSMC may approve a study to continue as planned or request more information or clarification from the investigator prior to approval. The PI of a study which has unresolved issues are required to submit a response within a timeframe set by the Committee, usually allowing for re-review at the next meeting. If a corrective and preventive action plan is
necessary, a timeframe will be set and a follow up schedule will be put into place to evaluate the corrective and preventive action plan.

The DSMC has the authority to require additional monitoring and/or more frequent reporting on study progress and serious adverse events, require the establishment of a DSMB, or require the appointment of a medical monitor or an ad hoc safety committee, external to the DSMC, during the study.

Upon completing the review, the DSMC will approve whether the study should continue as planned, require modification/amendment, or be placed on administrative hold with accrual temporarily suspended.

The DSMC may place trials on administrative hold (temporary suspension to accrual) for some of, but not limited to, the following reasons:

- Serious unexpected adverse event(s) that significantly alter the risk/benefit ratio
- Serious or multiple deficiencies in study conduct (e.g., lack of informed consent, violation of patient eligibility criteria, failure to report a serious adverse event, etc.).
- Lack of compliance with IND obligations
- New data suggesting the active protocol cannot achieve study objectives, or significantly altering the risk/benefit ratio
- Multiple major deficiencies in an internal or external audit or monitoring report
- Evidence of serious scientific misconduct or unsafe practices

Administrative hold of trials by the DSMC will be communicated to the Yale HRPP in writing. Serious issues concerning safety, compliance, or scientific misconduct are communicated to the YCC Clinical Research Oversight Committee. Decisions made by DSMC may be appealed by the PI to the YCC Director.

Trials being monitored by the YCC DSMC will remain under the YCC DSMC purview until a DSMC review has occurred that includes the research activity of the last subject who completed the intervention, or until the DSMC feels there are no patient safety concerns that require further monitoring. The DSMC will determine the length of continued DSMC review on a study-by-study basis.

2.4.5.2 Serious Adverse Events

Serious Adverse Events (SAEs) recorded in OnCore are reviewed at least monthly by an assigned DSMC reviewer. SAEs are reviewed individually as well as in aggregate to assess trends. If the DSMC observes toxicities that are unexpected and/or occurring at greater frequency than previously known or recognized, the DSMC may require additional monitoring and/or stop the trial due to safety concerns.

2.4.5.3 Deviations

Protocol-level and subject-level deviations recorded in OnCore are reviewed at least monthly by an assigned DSMC reviewer. Deviations are assessed for trends. If a protocol has a
disproportionate number of deviations, the DSMC may require a corrective and preventive action plan or additional monitoring.

2.4.5.4 Two-Stage Design with Stopping Rules

For investigator-initiated trials led by Yale that have a two-stage design with stopping rules, the Principal Investigator will submit a summary of progress to date outlining responses or other criteria used in the protocol to determine moving to the second stage of the trial. Prior to beginning accrual to the second stage, the DSMC will review the summary and data and approve continuing as planned.

2.4.5.5 Audit Review

When completing audit reviews, the DSMC will set the timeframe for the next internal audit. Typically, investigator-initiated trials, each Smilow Cancer Hospital Care Center and NCTN groups are audited annually, but the DSMC may adjust the audit schedule based on their review. For external audit reviews, the committee may require a corrective and preventive action plan and/or additional monitoring, if deemed necessary.

2.4.5.6 DSMC Recommendations

The Principal Investigator must implement recommendations from the DSMC expeditiously. When requested by the DSMC, the PI or their designee will respond in writing to the DSMC of the actions taken regarding the recommendations and the reasons for that decision.

The YCC Director will adjudicate any disagreements between the DSMC and Principal Investigator.

2.4.6 Data and Safety Monitoring Board (DSMB)

If the study is approved by the PRC on scientific grounds, the PRC Committee will determine if an independent DSMB is required for adequate subject oversight. Independent DSMBs are typically required for Phase III or large, randomized Phase II YCC IITs with comparative endpoints. If an independent DSMB is required, the PRC will request the following from the PI:

- Proposed frequency of meetings for the DSMB
- Proposed list of data items to be provided to the DSMB
- Nominate as members no fewer than three persons, providing information on the nominated DSMB members, including:
  - CV
  - list of current affiliations with pharmaceutical and biotechnology companies
  - name of the company
  - type of affiliation (e.g., stockholder, consultant)
  - any other relationship that could be perceived as a conflict of interest, related to the study and associated with commercial interests.

These nominations are subject to approval by the Yale Cancer Center DSMC Committee. The PRC will reserve the right to appoint additional members to the DSMB to include scientific expertise in topic areas relevant to the trial, such as biostatistics, ethics, or patient advocacy.
DSMB responsibilities will include the following:

- Review the entire study protocol, the data and safety monitoring plan, and the informed consent form(s), recommending changes to these, as appropriate.
- Recommend the initiation of subject recruitment only after final acceptance of the above documents.
- Identify the format, timing, and specific data parameters to be provided by study personnel for review by the DSMB during the study.
- At specified intervals over the course of the trial (at least twice yearly throughout the conduct of study with additional meetings as needed), review data on patient safety, efficacy, and accrual, including gender and minority inclusion, randomization, protocol compliance, retention, and data collection.
- Identify patient safety issues raised by ongoing review, informing the PI of these issues by written report. The PI will be responsible for expeditious distribution to all site PIs.
- Propose appropriate analyses, and identify and request from study investigators, any additional data required to fully evaluate safety issues and efficacy endpoints.
- At each meeting, reconsider the rationale for continuation of the study, based on all available information on accrual, progress of randomization, retention, protocol compliance, data management, safety and efficacy outcomes, as well as new information from other clinical trials, and make a recommendation for or against continuation of the trial.
- Provide the PI with written reports following each DSMB meeting. The study PI is responsible for sending reports to the DSMC and the Yale IRB, and to individual site PIs, who are required to distribute the report to the IRB of Record.
- Review and approve any release of outcome data.
- Review manuscripts of trial results prior to submission for publication or public presentation.

The content and structure of DSMB meetings are determined by each DSMB for a particular study, but should generally include three parts:

- An open session in which investigators and personnel involved with the clinical trial may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the DSMB. Issues discussed may include accrual, protocol compliance, and toxicity data.
- A closed session involving the DSMB and study statistical staff at which the statistician(s) should present and discuss the outcome results with the DSMB.
- A final closed session involving only DSMB members for discussion of the general conduct of the trial and all safety and efficacy results, and to come to a consensus about further recommendations or actions required, including recommendation for or against continuation of the trial.

Confidentiality Procedures:
No communication, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB, except as provided for in this policy. Outcome results are strictly confidential and must not be divulged to any non-member of the DSMB until the recommendation to release the results are accepted and implemented. Each member of the DSMB must sign a statement of confidentiality.

Conflict of Interest:
DSMB members are subject to the YCC policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and to appropriate Yale Cancer Center officials, in accordance with institution policies. Potential conflicts which develop during a member's tenure on a DSMB must also be disclosed. Conflict of interest can include professional interests, proprietary interests, and miscellaneous interests, as described in the NIH Grants Policy Statement and 45 CFR.
Part 94. Decisions concerning DSMB membership for individuals with potential conflicts of interest will be made in accordance with institutional policies.

2.4.6.1 Escalation

Serious issues concerning safety, compliance, or scientific misconduct are referred to the YCC Director. Decisions made by the DSMB may be appealed by the PI to the YCC Director.

2.4.7 Clinical Research Oversight Committee (CROC)

The Clinical Research Oversight Committee (CROC) is comprised of members of the YCC and SCH leadership. Appeals regarding decisions from the Protocol Life-Cycle Subcommittee and Protocol Review Committee (PRC) may be submitted to the CROC for initial review. The CROC review and recommendation on the appeal will be submitted to the PRC for their decision on the appeal. The PRC has final and absolute authority on all appeals related to the PRMS.

2.4.8 Office of Quality Assurance and Training

2.4.8.1 Internal Audit Program

The Office of Quality Assurance (QA) and Training (OQAT) is a resource that assists investigators at the Yale Cancer Center in conducting high-quality compliant clinical research. QA Specialists are available to consult with investigators on quality-related issues, such as Federal Regulations, Good Clinical Practice (GCP) or other protocol compliance issues, upon request. In addition, QA Specialists review trials using risk-based stratification, providing feedback on compliance and opportunities for systems improvements. The initial internal audit schedule is determined by the PRC based on the trial risk assessment at the time of initial study approval. The audits are conducted by the OQAT and reviewed by the DSMC.

The purpose of the audit program is:
- To assure patient safety by monitoring compliance
- To assure regulatory compliance by reviewing documentation of consent and adverse event reporting
- To assure scientific integrity by monitoring accuracy and completeness of data collection.

2.4.8.2 Monitoring

The Office of Quality Assurance and Training provides expertise for centralized monitoring of multicenter investigator-initiated clinical trials for which Yale is the lead site. Monitors are available to provide their expertise to ensure each study is conducted according to GCP guidelines and all other applicable regulations. They work closely with the YCCI Multicenter Unit Project Managers to act as a central coordinating site and deliver operational excellence for all studies under their purview.

Some of the various services provided by the monitors are listed below:

Site Initiation Visits
- Review operational aspects of the protocol with the investigator and clinical site staff
• Assist with providing detailed instructions for CRF/eCRF completion
• Review regulatory documents
• Discuss subject recruitment
• Review safety reporting
• Review handling of data queries
• Review drug and/or device management
• Review Good Clinical Practice standards

**Interim Monitoring Visits**
- Review informed consent form completion and process documentation
- Confirm HIPAA compliance
- Verify subject eligibility
- Monitor protocol violations/deviations
- Perform source documentation verification and CRF/eCRF data review
- Monitor adverse event and serious adverse event reporting
- Handle query resolution
- Evaluate reasons for screen failure or withdrawal
- Review regulatory documents
- Perform drug and/or device accountability

**Close-Out Visits**
- Perform final source documentation verification and CRF/eCRF data review
- Reconcile regulatory documents
- Finalize adverse event documentation, subject disposition and query resolution
- Perform final study drug and/or device accountability and return or destruction
- Review with the site staff their obligations following study termination

**Other**
- Assistance with protocol design and implementation
- Setup and coordination of protocol-specific Data and Safety Monitoring Boards (DSMBs)
- Development of protocol-specific Data and Safety Monitoring Plans
- Assistance with identifying and hiring contract monitors
- Completion of study start-up activities

### 2.4.9 OnCore

OnCore is a robust electronic software application that facilitates many aspects of the clinical research program. For the PRMS it provides a management tool for protocol review including the systematic tracking of committee activities and accrual monitoring. All YCC studies are entered into OnCore at the time of submission and all committee actions are tracked and maintained by support staff within the system. Study status changes, accruals, study and subject milestone dates, and IRB reviews are entered by CTO staff and the system is projected during committee meetings to facilitate the review process which includes data accuracy. Serious adverse events, protocol deviations, internal audits and observations, accruals and committee activity are tracked. OnCore provides electronic case report forms for investigator initiated studies.

### 2.4.10 Education & Training
The Office of Quality Assurance and Training coordinates a training program for all staff involved with oncology clinical trials. In addition to encompassing many standard topics, including but not limited to Good Clinical Practices (GCP), IRB Basics, Research Ethics and Misconduct, specific topics key to the understanding of compliance and safety are identified and addressed as required. Education sessions and training programs are held in coordination and collaboration with Yale University’s HRPP and the YCCI.

2.5 **Protocol Specific Data and Safety Monitoring**

2.5.1 **Overview**

The Principal Investigator is responsible for developing a protocol-specific DSMP that describes how the investigator intends to provide ongoing supervision and evaluation of the activities of the study, including whether new risks have been identified and whether appropriate progress is being made.

2.5.2 **Risk Assessment**

Each protocol is assigned a Risk Assessment score that determines the institutional auditing schedule. The Risk Assessment is conducted by the Office of Quality Assurance and Training and is recorded in OnCore.

2.5.3 **Monitoring Plan**

In addition to the institutional auditing plan defined by Risk Assessment, each trial is required to have a protocol-specific data and safety monitoring plan. This plan should be inclusive of the investigator’s plan to conduct study oversight activities.

The DSMP must document the procedures and means to protect the welfare and safety of subjects and to protect the integrity of the data. When the study sponsor is performing data and safety monitoring activities, the Yale investigator must provide a brief plan that describes how the local monitoring responsibilities will be integrated into the sponsor’s DSMP and accomplished by the Yale investigator and how the IRB reporting requirements will be met.

The type and degree of monitoring must be commensurate with the degree of risk involved, the size and complexity of the study, and should be appropriate to the study population and research environment. The plan must include provisions for data review and performance of safety reviews, at a specified frequency appropriate for the level of risk undertaken by research subjects. The plan must also include provisions for reporting Unanticipated Problems Involving Risks to Subjects or Others and Reportable Adverse Events to the IRB as required by IRB policy and/or other internal and external organizations.

2.5.3.1 **Multicenter Trials**

For YCC Multicenter Investigator-Initiated studies, the investigator is responsible for further defining PI oversight and coordinating center responsibilities. The Yale Principal Investigator is responsible for the coordination and safe conduct of the clinical study at all participating institutions, according to the policies, procedures and guidelines established by Yale University, the participating institutions and local and federal regulations.

Institutional support for investigator-initiated studies is two-tiered. The Multicenter Unit (MCU) provides project management support including but not limited to protocol development, eCRF design, training, regulatory support, maintenance of Trial Master File, and coordination support.
Yale Cancer Center Data and Safety Monitoring Plan

2.6 CONFLICT OF INTEREST

2.6.1 Yale Cancer Center Research Oversight Committees

The YCC Conflict of Interest (COI) procedures for all YCC Committee Members and Staff are as follows:

- At the start of each meeting the Committee Chair shall ask members and staff to identify any conflict of interest they may have with a protocol scheduled for review on the meeting agenda. Committee members and staff must recuse themselves from deliberations or decisions concerning protocols in which they have, or appear to have, a conflict of interest. This includes any actual or anticipated direct involvement in the design, conduct, or reporting of a study that is being reviewed, or other interests that might affect or appear to affect their objectivity in reviewing the study. However, at the discretion of the Committee Chair, members/staff may provide information and answer questions regarding the research prior to the recusal.

- Once a conflict of interest has been identified, the YCC Committee Chair shall evaluate the conflict and discuss it with the committee member or staff person to evaluate the individual’s ability to take part in protocol review and approval activities that may be influenced by the individual’s interest. The individual will be directed to recuse themself from deliberations or decisions when considering any research project or report for which a real or potential conflict has been identified. The Committee Chair shall consult with the Provost’s Office or the Yale IRB regarding further actions when appropriate.

- In the event the Committee Chair has a conflict of interest, the Committee Vice Chair shall evaluate the conflict and make a recommendation for the Committee Chair to recuse themself. In the event that both the Committee Chair and the Vice-Chair have a conflict of interest, a non-conflicted member shall serve in this capacity.

- The committee meeting minutes shall include any identification of conflict or appearance of conflict and the Committee’s decision or action taken related to that conflict.

- Committee members and staff may choose to recuse themselves from the Committee discussion and/or vote, even if no actual conflict exists, if it will avoid the appearance of a conflict of interest.

2.6.2 Institutional Committees

All investigators must report potential conflicts of interest to Yale University annually and in the event of any material change from the annual disclosure. The Yale University policy on conflict of interest can be found at: http://your.yale.edu/policies-procedures/other/yale-university-policy-conflict-interest.

3 PLANS FOR ASSURING DATA ACCURACY AND PROTOCOL COMPLIANCE

3.1 RISK ASSESSMENT

At the time of PRC review, a risk assessment is conducted by the Office of Quality Assurance and Training.
The risk assessment considers the following factors:

- Complexity of the Study Design
- Types of Study Endpoints
- Clinical Complexity of the Study Population
- Locations where study is being conducted
- Relative Experience of the Investigator and of the Sponsor with the Investigator
- Electronic Data Capture
- Relative Safety of the investigational product or intervention
- State of the study
- Quantity of the data

This risk assessment determines the institutional auditing schedule as described below.

<table>
<thead>
<tr>
<th>Risk Assessment Score</th>
<th>Initial Audit</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10</td>
<td>100% of the first 2 subjects accrued, regulatory, pharmacy for investigational products</td>
</tr>
<tr>
<td>7-10</td>
<td>Consent &amp; eligibility for first 2 subjects, regulatory</td>
</tr>
<tr>
<td>&lt; 7</td>
<td>Random (1 trial per month; rotate YCC DARTs): Consent &amp; eligibility for 2 subjects, regulatory</td>
</tr>
</tbody>
</table>

All studies approved by the IRB have a risk assessment checklist completed by the Office of Quality Assurance and Training. A monthly Risk Assessment report is generated using OnCore and trials which meet the review trigger are identified.

### 3.2 Auditing

Audits are conducted by the Office of Quality Assurance and Training, including for cause, preparatory and routine audits. Audits can be on individual protocols, targeted to specific components, or focused on the conduct of the Coordinating Center or an individual site. Audit findings are discussed with the Principal Investigator and then subsequently reviewed by the YCC DSMC. The results of the audit are reported to the PI and to the DSMC Committee, with comments and recommendations for a corrective and preventive action plan, if appropriate.

Items audited may include:

- Consent form(s) for signatures, dates, and validity of form
- Protocol compliance
- Eligibility criteria
- Adherence to treatment plan as written in the protocol
- Adverse event grading, documentation, and reporting
- Response evaluations
- Compliance with all regulations, Yale University policies, and IRB guidelines
- Accuracy of data entry
Investigational Product or device accountability

A notification letter is sent via email to the PI, Study contact(s) and Department Administrator(s). After the notification is sent, a QA auditor will reach out to schedule an introductory meeting.

The introductory meeting’s purpose is to:

- Review purpose of QA review and process
- Gather basic study information through discussion with PI and team
- Understand trial and study conduct to help guide audit
- Set expectations and answer questions

After the review, the QA auditor will reach out to schedule an exit meeting with the PI and team. The exit meeting’s purpose is to:

- Review preliminary observations
- Get clarifications from PI and team on any remaining questions
- Acknowledge best practice and provide guidance and feedback on areas that may need improvement

After the exit meeting, a final summary report will be sent to the PI and appropriate members of the research team. The summary report will include:

- Observations with citations to the Code of Federal Regulations (CFR) and International Conference on Harmonization (ICH) GCP, as applicable
- Discussion from exit meeting
- Recommendations or Required Responses, as applicable

After review, the DSMC may recommend a subsequent audit schedule based upon the following:
### 4 ASSURING COMPLIANCE WITH REQUIREMENTS FOR ADVERSE EVENT REPORTING

#### 4.1 OVERVIEW

All studies must have a structured adverse event determination, monitoring and reporting system, and procedures for referring and/or treating subjects experiencing adverse events.

By regulation (21 CFR Part 312.32), an SAE is defined as an adverse event that results in the following outcomes:

- is fatal or life-threatening (i.e., results in an immediate risk of death)
- is persistently or significantly incapacitating or substantially disrupting the ability to conduct normal life functions
- requires or prolongs hospitalization
- is a congenital anomaly/birth defect

This definition also includes any other event the investigator judges to be serious, or which would suggest a significant hazard, contraindication, side effect, or precaution.

Studies must include a proposed schedule for reporting adverse events to the DSMB (if one is established), the IRB of record, study sponsors, and/or the National Institutes of Health (NIH)/FDA.
• If the proposed protocol has additional clinical sites besides the Yale Cancer Center, the protocol should describe procedures by which the PI will notify all sites regarding SAEs, as identified by the investigator, the DSMP, and/ or DSMB, if one is established. Furthermore, the protocol must specify procedures for individual sites to report SAEs either directly to the appropriate oversight authorities, or through the study PI. In all cases, the study PI must be informed of all SAEs, and will be responsible for the overall safety of the trial.

• In cases where the IND is held by a Yale investigator, the Yale investigator will be responsible for reporting all SAEs in timeframes consistent with 21 CFR Part 312.32.

• In specific cases where an outside agency is the sponsor of an investigational agent, i.e., holder of an Investigational New Drug [IND] application, the PI’s must submit individual Adverse Event Reports to the IND holder, in accordance with agency and FDA regulations.


The Yale Cancer Center follows the guidelines provided by the National Cancer Institute (NCI) for reporting adverse events for drugs.

4.2 IRB ADVERSE EVENT REPORTING POLICY

PIs are responsible for promptly reporting adverse events to the Yale IRB which are 1) deemed unexpected in nature, specificity, severity or frequency; 2) related or possibly related to participation in the research, and 3) suggests that the research places the subject(s) or others at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized. Adverse events must meet all three criteria to require prompt reporting to the Yale IRB. Internal (occurring at a study site under the jurisdiction of the Yale IRB) adverse events that may require a temporary or permanent interruption of study activities by the PI or sponsor to avoid potential harm to subjects should be reported to the IRB immediately (if possible), followed by a written report to the IRB no more than five (5) calendar days after the PI becomes aware of the event. External (occurring at a study site not under the jurisdiction of the Yale IRB) adverse events should be reported via written report to the IRB within 15 calendar days of the PI becoming aware of the event if the event requires an immediate change to the protocol or consent documents. Prompt reporting of adverse events to CIRB or other external IRBs are done according to their written policies and procedures.

4.2.1 IND Safety Reports

Per the Code of Federal Regulations (CFR) (21 CFR Part 312.32), it is the responsibility of the sponsor of a study being conducted under an Investigational New Drug (IND) to notify the Food and Drug Administration (FDA) and all participating investigators in an Investigational New Drug Safety Report (INDSR) of suspected adverse reactions associated with the use of the study drug(s) that are both serious and unexpected in nature, from clinical trials or any other source. Suspected adverse reactions are those events where there is a reasonable possibility that the study drug caused the adverse event.

When a Principal Investigator (PI) serves in the role of Sponsor-Investigator, that PI is also responsible for notifying the FDA and all participating investigators of any potential serious suspected adverse reactions via INDSRs in accordance with 21 CFR 312.32. Sponsors and/ or their designees issue INDSRs via method of their
preference such as email, facsimile, mail, or web-based portals. The method of distribution will be communicated prior to or at the time of the Site Initiation Visit or equivalent. Following initial Institutional Review Board (IRB) approval, the Yale Cancer Center (YCC) Regulatory Designee(s) will ensure they are in receipt of any INDSRs and will file reports in the regulatory binder (or indicate the filing location via note to file in the regulatory binder). INDSRs will be accepted by the Regulatory Designee from the time of initial IRB approval of a study through such time that either: the study has been permanently closed with the IRB of record, the study has permanently closed to enrollment with no subjects enrolled, or the study has permanently closed to enrollment and all subjects are deceased, whichever comes first.

The Investigator’s Brochure (IB) for an investigational new drug includes safety data through the cut-off date listed in the IB. The most recent version of the IB is approved by the Institutional Review Board (IRB) of record, as applicable, with the initial IRB approval. INDSRs received from the sponsor or their designee during study start-up that account for reports received between versions of IBs, also known as the Gap Listing, will be filed in the regulatory binder by the Regulatory Designee.

Only those external INDSRs that meet the below reporting criteria should be issued to the PI and Regulatory Designee(s):

- The event is unexpected in nature,
- The event is related or possibly related to participation in the research, and
- The event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

YCC recognizes that the sponsor is responsible for evaluating the overall importance of the event and determining if the event meets the criteria specified above and is therefore considered an unanticipated problem in accordance with Office of Human Research Protection (OHRP) guidance from January 2007. The sponsor is responsible for determining if an event warrants additional action such as a revision to study documents or a suspension of enrollment.

As a single site participant, the PI is not able to adequately review individual external event(s) to determine severity or relatedness to participation in the research nor is the PI able to determine if further action should be taken. For studies where a PI does not hold the IND, local review and assessment of external INDSRs will not occur unless the sponsor explicitly states that the event is considered an unanticipated problem.

If the sponsor determines that an external event meets the criteria for unanticipated problem, the INDSR must be accompanied by a clear explanation of why the event or series of events has been determined to meet the criteria for unanticipated problem, a description of proposed protocol, consent form and/ or Investigator’s Brochure changes and any corrective actions to be taken by the PI in response to the external event, and aggregated data and an analysis or summary to explain the significance of the event or series of events. This information will be filed in the regulatory binder.

If the sponsor determines that an external event meets the criteria for unanticipated problem involving risks to participants or others and warrants a change to the study documents or if a change to the study documents is directed by a monitoring entity because of an INDSR, this will be reported to the IRB of record as per their written policies and procedures. When changes to the study documents are warranted, the PI and study team will be notified of these changes at the time of amendment approval and this documentation will be maintained in the regulatory binder by the Regulatory Designee(s).
4.3 Yale Cancer Center SAE Internal Reporting and Review

The CTO coordinates completion and submission of serious adverse event (SAE) and protocol deviation reports to the IRB and sponsors. Investigators and research staff identify SAEs and ensure that SAE information is entered into OnCore in a timely fashion. A report is generated on paper or from the electronic data capture system for investigator review and sign-off. Clinical Research Coordinators (CRCs) receive and distribute signed SAE reports to the PI, regulatory staff and other relevant members of the study team and are responsible for updating OnCore with new information provided by the investigator. The Regulatory staff are responsible for reviewing the SAE entry in OnCore and for submitting the report to the IRB when IRB submission criteria have been met. SAE reports submitted to the NCI (i.e., for NCTN group studies and Cancer Therapy Evaluation Program (CTEP) trials) are entered into OnCore and NCI’s AdEERS system by a CRC. The PI reviews all SAE reports. SAEs at collaborating Smilow Cancer Hospital Care Centers are reported to the CTO. Data from the report are entered into Oncore. SAE summary reports are available in OnCore and are reviewed monthly by YCC’s DSMC.

4.4 Multi-center Unit Reporting

A. Reporting AEs from Participating Sites to the Multi-Center Unit Project Management team

Participating sites are responsible for tracking all AEs for participants at their site. At the beginning of the trial, sites will be provided a template AE log that can be used if an equivalent site-specific procedure is not in place. Site investigators are required to determine attribution of any AEs at their site. All AEs will be entered into the electronic data capture (EDC) system by the appropriate study staff in a timely manner to ensure the study team has access to up-to-date safety information throughout the trial. AE logs and source data will be reviewed during both onsite and remote monitoring visits by the study monitor.

B. Reporting SAEs from Participating Sites to the Multi-Center Unit

Sites will be instructed that all SAEs need to be reported to the Multi-Center Unit as soon as possible, and no later than 24 hours from the onset of event (or the study team becoming aware of the event). SAEs and accompanying documents (if applicable) will be sent to the sponsor team members designated in the protocol or other study related documents, using the SAE form provided by the MCU project manager. In order to adhere to the 24-hour reporting deadline, sites are instructed to complete and return the form with all available details. It is acceptable for some of the information to be incomplete if it is not yet known. All additional information learned after the first 24 hours will be sent on the same form in a subsequent follow-up report to be filed as soon as information is available. Multiple follow-up reports are acceptable as new information is gathered.

In many cases, there will be specific situations that require reporting events as SAEs even if the event does not meet the definition. In these cases, details will be written into the protocol and emphasized by the MCU project manager through procedure manuals, investigator binders, and Site Initiation Visits (SIVs) as applicable.

SAEs will be documented on the AE log as well as within the EDC system. Sites are instructed to complete SAE data entry in an expedited manner to ensure the MCU project manager has access to up-to-date safety information throughout the trial.

C. Reporting AEs from Multi-Center Unit to External Review Entities

In some cases, the protocol will identify external entities that require review of AE data. These can include, but are not limited to, data safety monitoring committees, pharmaceutical companies supplying investigational product for the trial, institutional review boards, funding agencies, FDA or other safety oversight entities. The MCU project manager will provide AE reports via the EDC system whenever possible. In studies where this is not possible an AE reporting plan will be in place prior to trial commencement.
For studies conducted under an IND administratively managed by the YCCI IND Manager, in conjunction with the PI, the MCU project manager will provide a summary report of all AEs at the time of the IND annual report to the IND Manager for filing.

D. Reporting SAEs from the Multi-Center Unit to External Review Entities
When the Multi-Center Unit receives an SAE form from a participating site, it will be reviewed by the project team, including the Sponsor PI. If the sponsor PI is not immediately available for physical signature on the SAE reporting form, documentation of Sponsor PI awareness (i.e., email or phone call documentation, etc.) will be acceptable until a signature can be obtained.

After discussion with the Sponsor PI, a determination will be made regarding the need for expedited external reporting based on the protocol requirements. External SAE reporting is protocol specific and all reporting decisions should be made after reviewing the relevant protocol sections.

Expedited FDA reporting, as required for investigator initiated multi-center trials being conducted under an IND, will be completed by the MCU Project Manager. Required documentation, including but not limited to, the completed MedWatch Form FDA 3500A and collated supporting documentation, will be completed by the MCU Project Manager and submitted to the FDA. Expedited reports should be sent in a timeframe specified by all applicable regulations. Copies of all submitted documents, as well as all correspondence, will be filed in the Trial Master File (TMF).

All SAEs that are immediately reportable to the FDA also need to be reported to the sites participating in the study. These reports are sent from the MCU Project Manager to the site investigator(s) and responsible site staff within the required regulatory timeframes.

For studies conducted under an IND handled by the YCCI IND Manager, the MCU project manager will provide a summary report of all SAEs at the time of the IND annual report to the IND Manager for filing with the FDA. The MCU Project Manager will identify those SAEs that were reported expeditiously as well as those that are being newly provided to the FDA.

E. Updated Investigator Brochures and IND Safety Reports
The MCU Project Manager is responsible for tracking all updated Investigator’s Brochure(s) (IBs) and IND Safety Reports. All IND Safety Reports must be logged by the MCU Project Manager and reviewed by the Sponsor PI in a timely manner. Reviewed IND Safety Reports are sent to sites at a minimum of once a month to be processed per the sites local policy. Updated IBs are distributed to sites only after they are reviewed by the sponsor project team.

5  PROCESS FOR ASSURING THAT ANY ACTION RESULTING IN A TEMPORARY OR PERMANENT SUSPENSION OF NCI-FUNDED CLINICAL TRIAL OR TRIAL INVESTIGATOR IS REPORTED TO THE NCI PROGRAM DIRECTOR RESPONSIBLE FOR FUNDING THE TRIALS, AND OTHER APPROPRIATE AGENCIES.

All temporary or permanent closure determinations made by the IRB or Yale Cancer Center due to non-compliance or safety concerns will be reported by the Office of Research Projects to the NCI Grant Program.
Director on NCI-sponsored clinical trials (non-NCTN studies). These closures will be reported to the NCI Program Director within 10 working days of the determination.
### APPENDIX I: PROTOCOL REVIEW COMMITTEE REVIEW REQUIREMENTS BY PROTOCOL TYPE

<table>
<thead>
<tr>
<th>Protocol Type</th>
<th>Sponsor Type</th>
<th>Review Required</th>
<th>Review Type</th>
<th>Scientific Review</th>
<th>Biostatistician Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic Interventional</td>
<td>National</td>
<td>Yes</td>
<td>Expedited&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 Reviewer</td>
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<tr>
<td></td>
<td>Externally Peer-Reviewed</td>
<td>Yes</td>
<td>Expedited&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 Reviewer</td>
<td>N/A</td>
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<tr>
<td></td>
<td>Institutional</td>
<td>Yes</td>
<td>Full Board</td>
<td>2 Reviewers</td>
<td>1 Reviewer</td>
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<tr>
<td></td>
<td>Industry</td>
<td>Yes</td>
<td>Full Board</td>
<td>1 Reviewer</td>
<td>N/A</td>
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<tr>
<td>Non-therapeutic Interventional, i.e., diagnostic, staging, behavioral, etc.</td>
<td>National</td>
<td>Yes</td>
<td>Expedited&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 Reviewer</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Externally Peer-Reviewed</td>
<td>Yes</td>
<td>Expedited&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 Reviewer</td>
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</tr>
<tr>
<td></td>
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<td>Full Board</td>
<td>2 Reviewers</td>
<td>1 Reviewer</td>
</tr>
<tr>
<td></td>
<td>Industry</td>
<td>Yes</td>
<td>Full Board</td>
<td>1 Reviewer</td>
<td>N/A</td>
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<td>Non-therapeutic Non-Interventional, i.e., Quality of Life Studies, etc.</td>
<td>National</td>
<td>Yes</td>
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<tr>
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<td>Externally Peer-Reviewed</td>
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<td>Administrative&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Ancillary or Correlative, i.e., specimen/data collection&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Yes</td>
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<td>1 Reviewer</td>
<td>N/A</td>
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<td>Full Board</td>
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<tr>
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<td>Yes</td>
<td>Full Board</td>
<td>1 Reviewer</td>
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</tr>
<tr>
<td>Observational including cancer patients and healthy populations</td>
<td>National</td>
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<tr>
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<td>N/A</td>
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<tr>
<td></td>
<td>Industry</td>
<td>Yes</td>
<td>Administrative&lt;sup&gt;2&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Exempt from Review: Any Non-hypothesis driven research&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Retrospective chart review, biorepository, tissue bank, Single Patient IND</td>
<td></td>
<td></td>
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</tbody>
</table>

1 Expedited Review: Submissions are reviewed by the chair, vice-chair, or designee for prioritization. The risk assessment is conducted by the Office of Quality Assurance and Training and the data and safety monitoring plan is reviewed and approved by the reviewer at time of review. Approved submissions are listed on the Protocol Review Committee (PRC) meeting agenda for notification to PRC membership.

2 Administrative Review: Submissions are reviewed administratively by the PRC Regulatory Analyst. The risk assessment is conducted by the Office of Quality Assurance and Training and the study is assigned a data and safety monitoring plan. Acknowledged submissions are listed on the PRC meeting agenda for notification to PRC membership.

3 Only studies that can be linked to individual participant data will be reported to the NCI.