

Data and Safety

Monitoring Plan

Oregon Health & Science University

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Knight Cancer Institute
Oregon Health & Science University

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ABBREVIATIONS

CRRC	Clinical Research Review Committee
CTEP	Cancer Therapy Evaluation Program
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
IIT	Investigator Initiated Clinical trial
IND	Investigational New Drug
IRB	Institutional Review Board
KCTO	Knight Clinical Trials Office
NCI	National Cancer Institute
NIH	National Institutes of Health
OHSU	Oregon Health & Science University
UP	Unanticipated Problem

INTRODUCTION

The Oregon Health & Science University (OHSU) Knight Cancer Institute places the highest priority on ensuring the safety of patients participating in clinical research and the integrity of the clinical trial data. The Director of the OHSU Knight Cancer Institute and the Knight Cancer Institute Associate Director of Clinical Research are ultimately responsible for and provide administrative oversight of the data and safety monitoring activities related to clinical trials conducted within the Knight Cancer Institute. Other groups with responsibilities for data and safety monitoring include the Knight Clinical Research Review Committee (CRRC), the Knight Data and Safety Monitoring Committee (DSMC), OHSU Institutional Reviews Board (IRB), Knight Clinical Trials Office (KCTO), clinical trial-specific data safety and monitoring boards (DSMBs), the principal investigators of NIH grants and contracts supporting clinical trials, and, most importantly, the principal investigator of each clinical trial. See Appendix A for the organization of the OHSU Knight Cancer Institute data and safety monitoring activities.

This document outlines the plan established by the OHSU Knight Cancer Institute for the oversight of cancer related clinical trials. This plan outlines the elements required to ensure the safety of clinical trial participants, the accuracy and integrity of the data and the appropriate modification of clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be concluded successfully.

The Knight Cancer Institute Data Safety and Monitoring Plan (DSMP) follows the National Cancer Institute (NCI) policy for Data and Safety Monitoring of Clinical Trials¹. For the purposes of this plan the NCI definition of a clinical trial is being used:

“A prospective clinical trial involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these clinical trials may be patients with cancer or people without a diagnosis of cancer but at risk for it.

- ***Molecular or imaging diagnostics-*** *a study is considered to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. In this way the information from the diagnostic may have an impact on some aspect of outcome, and assessment of this impact may be a key goal of the trial. By contrast, studies that do not use information from the diagnostic test in any manner that can affect the outcome of study subjects, but whose objective is only the gathering of data on the characteristics of a new diagnostic approach, are not clinical trials and are not covered by this data and safety monitoring plan, unless performing the diagnostic test itself imposes some risk on study subjects.*
- ***Behavioral clinical trials-*** *interventions whose goals are to increase behaviors (e.g. cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life (e.g., among cancer survivors) and reduce the negative sequelae of treatment. Interventions may pertain to cancer prevention, early detection, treatment, and survivorship. Observational studies and those that do not test interventions are not clinical trials.”*

¹ <http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm>

For phase I, II and III clinical trials, the method and level of monitoring will correspond with the degree of risk involved in participation and the size and complexity of the clinical trial. A formal, clinical trial-specific DSMB will be constituted for Phase III randomized clinical trials or other clinical trials depending chiefly on the anticipated level of risk. Data Safety Monitoring Boards may be constituted for other clinical trials for reasons including, but not limited to, level of risk, complexity, management of early stopping rules, or the need to obviate conflict of interest.

For most investigator-initiated National Institutes of Health (NIH) grant applications, the investigator may supply this OHSU Knight Cancer Institute DSMP in the human subjects section of the grant application and describe how it applies to the specific clinical trial. The investigator may also tailor a plan for his/her specific clinical trial according to the level of risk to which participants in the clinical trial are exposed.

CATEGORIES OF CLINICAL TRIALS MONITORED AND LEVEL OF MONITORING

A variety of types of clinical trials are conducted by the Knight Cancer Institute. The level of monitoring is dependent on the type of study and the level of monitoring conducted by an outside entity. The categories of clinical trials monitored and the level of monitoring conducted are outlined below.

Sponsor: Industry

The Knight CRRC conducts full board reviews for all industry-sponsored clinical trials.

The industry sponsor is responsible for monitoring the clinical trial. Data and safety monitoring is not performed by the Knight DSMC for these clinical trials, but they are eligible for audit by the Knight Cancer Institute auditing team.

Sponsor: NCI Cooperative Groups

The Knight CRRC conducts expedited reviews of clinical trials sponsored by NCI Cooperative Groups because the clinical trials were peer-reviewed.

Clinical trials sponsored by the NCI Cooperative Groups are monitored by long-standing and established data and safety monitoring committees at the cooperative group level. These cooperative group clinical trials are not monitored by the Knight DSMC, but are eligible for audit by the Knight auditing team.

Sponsor: Local, Investigator Initiated Clinical trials

The Knight CRRC conducts full board reviews for all local, investigator initiated clinical trials regardless of funding mechanism.

Local, investigator initiated Phase I and Phase II clinical trials must include specific, detailed plans for data and safety monitoring. The principal investigator is required to closely monitor his/her clinical trial and to submit safety and data monitoring reports to the Knight DSMC on a regular basis (quarterly for Phase I clinical trials and twice-yearly for Phase II clinical trials).

Phase III randomized clinical trials must be monitored by a clinical trial-specific DSMB. The DSMB must be described in the protocols data and safety monitoring plan and must be approved by the Knight CRRC and the OHSU IRB. Other studies may also utilize a DSMB at the

discretion of the PI or reviewing committee(s). Reports from the DSMB should be submitted to the Knight DSMC and the OHSU IRB.

All local, investigator initiated clinical trials conducted in the Knight Cancer Institute will be audited by the Knight auditing team.

Multicenter Investigator Initiated Clinical trials

Knight Cancer Institute as a participating site –Unless specified in the protocol and/or required by the Knight CRRC or OHSU IRB as part of an approved monitoring plan, the Knight Cancer Institute auditing team will not provide oversight or monitoring for clinical trials conducted outside of the OHSU Knight Cancer Institute. The portion of the clinical trial conducted at OHSU will be reviewed for safety and audited according to Knight Cancer Institute standard audit and review procedures. Protocols where the Knight Cancer Institute is listed as a participating site must include a detailed clinical trial-specific DSMP specifying the responsibilities and oversight provided by the clinical trial coordinating center.

Knight Cancer Institute as a clinical trial coordinating center – Unless specified in the protocol and agreed upon by the OHSU IRB, all participating sites must identify their IRB of record. The protocol will be submitted, reviewed, approved and conducted under the auspices of the IRB of record for each clinical trial site. The coordinating group will identify a protocol manager who is responsible for ensuring the Knight Cancer Institute Coordinating Center Policies and Procedures² are appropriately followed. Protocol specific data and safety monitoring for the entire clinical trial will be conducted by the Knight Cancer Institute DSMC according to the phase and risk level of the clinical trial.

PRINCIPAL INVESTIGATOR

The principal investigator of a clinical trial is ultimately responsible for every aspect of the design, conduct, and final analysis of the protocol. The principal investigator is responsible to ensure that:

- Protocol includes a DSMP and procedures for its implementation
- A clinical trial-specific DSMB is established, if required
- The clinical trial has a clearly delineated adverse event and unanticipated problem determination, monitoring and reporting system
- Protocol describes procedures for protection of human subjects
- A blinded clinical trial includes a description of the planned randomization scheme, and specific criteria and procedures for unblinding of treatment assignment, if required. If a DSMB is not proposed, the protocol should designate specific individuals with access to unblinded data.
- Complete and accurate safety and data monitoring reports are provided to the Knight DSMC in accordance with the required schedule

² Knight Cancer Institute Coordinating Center Policies and Procedures
<http://www.ohsu.edu/xd/health/services/cancer/research-training/shared-resources/clinical-research-management.cfm>

- Protocol describes a central coordination plan if more than one site is involved with conduct of the clinical trial
- The protocol and amendment(s) are submitted to the Knight CRRC and OHSU IRB for review and approval before implementation
- Adverse events, serious adverse events, unanticipated problems and protocol deviations are reported as required to applicable agencies and committees/boards.

KNIGHT CLINICAL TRIALS OFFICE

The KCTO provides oversight for the conduct of all cancer related clinical trials conducted at the Knight Cancer Institute. Responsibilities of the KCTO are as follows:

- Ensures centralized registration for all subjects consented into cancer related clinical trials
- Facilitates administrative review of initial protocol submission, protocol revisions and continuing reviews for all cancer related clinical trials
- Provides administrative support to the Knight CRRC
- Conducts routine and targeted clinical trial audits to ensure adherence with federal and state regulations, and institutional policies.
- Provides administrative support to the Knight DSMC
- Assists in the training of investigators and clinical trial staff in the development and conduct of clinical trials
- Develops Knight Cancer Institute-wide standard operating procedures and policies to support clinical trial conduct

DISEASE SITE GROUPS

The Knight Cancer Institute has established Disease Site Groups for disease areas with ongoing clinical trials activities. A chairperson is appointed for each Disease Site Group. The responsibilities of these groups include the evaluation of proposed clinical trials and determination of feasibility based on the assessment of fit with patient population, gaps in potential studies for particular patient populations, potential competing clinical trials and fit with mission of the Knight Cancer Institute. These groups also assess the ongoing clinical research activities including progress with meeting accrual goals.

CLINICAL RESEARCH REVIEW COMMITTEE

The Knight CRRC is a multidisciplinary committee charged with providing peer review of the scientific merit of all cancer-related clinical research. For the purpose of this committee “cancer-related” is defined as any study designed to diagnose, prevent, or treat cancer; or provide supportive care to patients with cancer. The goal of the Knight CRRC is to ensure that all cancer-related clinical research conducted at the Knight Cancer Institute is:

- Scientifically meritorious

- Appropriately designed
- Feasible for completion within the specified time frame
- Compliant with US Food and Drug Administration (FDA) and NIH guidelines for clinical trials
- Consistent with the priorities, goals and interests of the OHSU Knight Cancer Institute

Membership on the committee includes representatives from pharmacy, biostatistics, oncology nursing, radiation oncology, surgical oncology, medical oncology, pediatric oncology, hematologic malignancies, orthopedics and the KCTO (administrator). In the event that a committee member is key personnel (principal investigator, co-investigator, biostatistician, study coordinator, study investigational pharmacist, study nurse) for a clinical trial under review, or has any other conflict of interest (including but not limited to substantial financial interest in the clinical trial sponsor), that member must recuse by abstaining from committee review and discussion and leaving the room during committee deliberations. In the event that the Chair is the principal investigator for the clinical trial, the committee co-Chair or other designated senior committee member will oversee the committee deliberations and final decisions. If at any time additional expertise is required in the review of a clinical trial, non-members may be consulted at the discretion of the chair. The appointment of committee members is 2 years and is renewable. The Knight CRRC reports thru the Knight Cancer Institute Associate Director of Clinical Research to the Knight Director. The committee chair is appointed by the Knight Cancer Institute Associate Director of Clinical Research for a term of 2 years. The Knight CRRC meets twice monthly.

The Knight CRRC is not intended to duplicate or overlap with the responsibilities of the OHSU IRB or other institutional committees, nor is it intended to perform an auditing or data and safety monitoring function, but does work collaboratively with both of those committees to ensure human subjects protection and scientific integrity.

The level of Knight CRRC review is determined based upon clinical trial type and design. Clinical trials involving no therapeutic intervention or clinical trials that have undergone a prior oncology related peer review process are evaluated using an expedited review process. Clinical trials falling to this category include:

- cooperative group clinical trials
- NCI CTEP trials
- surveys or questionnaires,
- blood draws, or other low-risk tissue sampling (hair, urine, sputum),
- voice or video recordings,
- interventions of moderate exercise,
- research involving existing data, documents, pathologic or diagnostic specimens,
- behavioral, cognition or perception clinical trials

An expedited review consists of checks for consistency between the protocol, the informed consent form and lay summary, and a check that a DSMP is provided. If deemed appropriate during administrative review, the study documents are sent to the biostatistician for review. Once the committee chair, or designee, approves the submission, it is sent on to the OHSU IRB. If significant issues are noted upon expedited review, the clinical trial undergoes full committee

review. The outcomes of expedited reviews are reported in writing to the full committee at the next Knight CRRC meeting.

Full committee review is required for clinical trials that have not undergone a prior oncology related peer review process and involve therapeutic interventions, including cancer-directed chemotherapy, biologic therapy, radiation therapy, or surgical intervention; clinical trials involving higher-risk tissue sampling (i.e., bone marrow or sampling requiring any type of anesthesia); and clinical trials involving agents available over the counter.

Full committee review consists of a scientific, statistical, pharmacy and administrative review of each clinical trial protocol. The DSMP associated with each clinical trial is also reviewed for appropriateness. Each review is discussed at the committee meeting and feedback is provided to the principal investigator in writing. Possible outcomes from the committee include 1) protocol approved, 2) protocol approved pending changes, or 3) protocol disapprove and may not proceed. Once approval, including pending changes required to secure approval, is issued, the study may proceed to the IRB for review. In order to help ensure sound scientific merit throughout the life of the clinical trial, all protocol amendments are reviewed by a committee administrator. Amendments that have a potential for substantively affecting the scientific integrity of the clinical trial undergo full committee review; this determination is made by the committee administrator in consultation with the committee chairperson, as required.

Administrative support of the Knight DSMC (paperwork, meeting coordination, meeting minutes) is provided by the KCTO. Meeting minutes reflect attendees, substantive issues discussed, voting results and members abstaining due to conflict of interest.

In addition to scientific review, the Knight CRRC is responsible for providing oversight of the scientific progress of interventional, therapeutic clinical trials that are open to enrollment. This evaluation includes the assessment of accrual rates and feasibility for completion within a reasonable timeframe to ensure that the scientific aims of the clinical trial can be met. Monitoring of clinical trial accrual is initiated once a clinical trial has been OHSU IRB approved and open for enrollment for at least 12 month. Criteria utilized in the assessment of reasonable clinical trial progress include: total accrual to date, average annual accrual, and accrual in the last 12 months. If each of these 3 categories is below 50% of expected accrual, the Knight CRRC queries the investigator to determine the reason for low accrual. If a scientific rationale is not provided or accrual challenges cannot be mitigated then protocol are closed to new subject accrual. The Knight CRRC has the authority to close clinical trials to enrollment based on low accrual. Additional information on this process is available in the Knight Cancer Institute Standard Operating Procedure for the Knight CRRC Study Closure Process³.

DATA AND SAFETY MONITORING COMMITTEE

The Knight DSMC is a multidisciplinary committee charged with overseeing monitoring of the safety of clinical trial participants, protocol adherence, clinical trial progress and the validity and integrity of clinical trial data for all clinical research conducted at OHSU Knight Cancer Institute. The committee chair is appointed by and reports thru the Knight Cancer Institute

³ Knight Cancer Institute Standard Operating Procedure for the Knight CRRC Study Closure Process
<http://www.ohsu.edu/xd/health/services/cancer/research-training/shared-resources/clinical-research-management.cfm>

Associate Director of Clinical Research to the Knight Director for a term of 2 years. The committee meets on a monthly basis to review the progress and safety of all ongoing interventional clinical research trials not monitored by an outside source; the Knight DSMC does not routinely oversee clinical research trials monitored by another entity including cooperative group clinical trials, industry sponsored clinical trials or clinical trials with a clinical trial-specific DSMB. The Knight DSMC also does not oversee non-interventional clinical trials. The Knight DSMC has the authority to require clinical trial protocol amendments, enrollment suspensions or termination of any research activities under its jurisdiction. Appropriate communication with relevant parties, including but not limited to the OHSU IRB Chairperson or designee occurs with any required change to the research.

The committee is made up of physician-investigator members of the Knight Cancer Institute, administrators of KCTO, biostatistician, research pharmacist, research nurses and study coordinators. A term of membership is 2 years and is renewable. In the event that a committee member is key personnel (principal investigator, co-investigator, biostatistician, study coordinator, study investigational pharmacist, study nurse) for a clinical trial under review, or has any other conflict of interest (including but not limited to substantial financial interest in the clinical trial sponsor), that member must be recused by abstaining from committee review and discussion and leaving the room during committee deliberations. In the event that the Chair is the principal investigator for the clinical trial, a designated senior committee member will oversee the committee deliberations and final decisions. If at any time additional expertise is required in the review of a clinical trial, non-members may be consulted at the discretion of the chair.

Ad hoc meetings may be convened when necessary, for urgent concerns. Administrative support of the Knight DSMC (paperwork, meeting coordination, meeting minutes) is provided by the KCTO. Meeting minutes reflect attendees, substantive issues discussed, voting results and members abstaining due to conflict of interest.

The frequency of DSMC monitoring depends on the level of risk of the clinical trial as summarized in Table 1 below.

Table 1: Monitoring and Auditing Activities of Local, Investigator-Initiated Trials

Study Type	Monitoring Frequency	Auditing
Pilot/Phase I	Quarterly reports to the Knight DSMC	At least yearly
Phase II/III	Half-yearly reports to the Knight DSMC	At least yearly

If a protocol is identified by the Knight CRRC or DSMC as being high risk and/or needing an alternate review schedule, a protocol specific plan will be developed. Data safety and monitoring activities continue from the time the protocol is OHSU IRB approved and active, to the time when all subjects have completed their treatment and all are beyond the time point at which clinical trial-related adverse events would likely be encountered. The DSMC does not monitor non-interventional clinical research.

For each DSMC clinical trial review, a summary of toxicity and accrual information is provided by the principal investigator in accordance with the following data elements:

- The expected and actual numbers of patients enrolled to date (local and national if multi-center clinical trial)
- Number of patients treated
- Description of any changes to the clinical trial design since the last DSMC review
- Exceptions in eligibility or treatment
- Dose tier for each patient, for Phase I clinical trials
- Treatment arm and best response to treatment (dependent on study endpoint) for each patient, for Phase II and III clinical trials
- Cumulative summary of adverse events with type and grade for each patient (Grades 3-5). Events of Grade 1 or 2 severity or temporal nature of event to study drug dosing may be requested depending on the clinical trial.
- List of dose limiting toxicities
- List of adverse events of interest as defined by the protocol
- List of all unanticipated problems (UPs) reported to the OHSU IRB (cumulative)
- List of all protocol deviations reported to the OHSU IRB (cumulative)
- Significant literature reporting developments that may affect the safety of participants or the ethics of the clinical trial
- Results of any interim analyses required by the protocol
- Copies of abstracts or papers written using clinical trial data

The committee may vote to take one of the following actions for each protocol reviewed:

- Full Approval: enrollment may continue; no outstanding questions regarding clinical trial data
- Conditional Approval: enrollment may continue conditional upon satisfactory response by the principal investigator to Knight DSMC concerns regarding clinical trial data
- Suspension: enrollment immediately suspending pending principal investigator response to Knight DSMC concerns regarding clinical trial data
- Closure: clinical trial closed due to unacceptable toxicity or other clinical trial data

The Knight DSMC also oversees the review of subject safety and data quality as assessed through the Knight Cancer Institute auditing function. All cancer-related clinical trials are eligible for an audit; however, emphasis is placed on those clinical trials that are not monitored by an outside entity. The Knight DSMC oversees the audit planning and the review of audit findings. If audits are conducted by external parties, the Knight DSMC reviews those findings either through the formal audit report provided by the external auditing entity, if available, or the principal investigator's report of any findings communicated during the audit process.

Through its review of audit data, the Knight DSMC has the authority to require clinical trial protocol amendments, enrollment suspensions or termination of any research activities under its jurisdiction. The Knight DSMC also has the authority to temporarily suspend enrollment in a clinical trial if the principal investigator does not provide a response to an audit within the

timeframe required by the Knight Cancer Institute Audit Plan. Appropriate communication with OHSU IRB Chairperson or delegate occurs with any required change to the research.

INSTITUTIONAL REVIEW BOARD

Following Knight CRRC approval, all protocols are forwarded to the OHSU IRB. OHSU has four IRBs which collectively cover all scientific research review at OHSU. The OHSU IRB Chair and Co-chair oversee the 4 boards. Members are appointed to these boards by the Provost for a term of 3 years with the option of renewal.

In addition to the 4 IRBs, there are two IRB leadership committees. The OHSU IRB Chair's Advisory Council, composed of investigators and administrators, sets policies and procedures for the institution and considers institutional best practices. The OHSU IRB Leadership Team, composed of the IRB Chairs, the Chief Integrity Officer, and the ORIO Associate and Assistant Directors, and has responsibility to 1) address complex human subjects protection issues, 2) investigate allegations of serious non-compliance; and 3) provide guidance for specific complicated and/or controversial protocol reviews. The OHSU IRB Leadership Team does not have formal decision-making authority but makes recommendations and refers issues back to the OHSU IRBs and Institutional Official.

All OHSU IRBs are registered with the Office for Human Research Protections and are associated with the OHSU Federal Wide Assurance (FWA00000161).

DATA AND SAFETY MONITORING BOARDS

A formal clinical trial-specific DSMB will be constituted for Phase III randomized clinical trials depending chiefly on the anticipated level of risk in accordance with the NCI Policy for Data and Safety Monitoring of Clinical trials⁴. DSMBs may be constituted for other clinical trials involving particular risk, complexity, likely decisions about early stopping or the need to obviate conflict of interest. The Knight CRRC or OHSU IRB may also require that a DSMB be established for high-risk Phase I or Phase II investigator-initiated clinical trials.

The DSMB is established prior to clinical trial activation by the principal investigator. The DSMB members are appointed for a fixed term of service. Members may be within or outside the Knight Cancer Institute, but a majority of the DSMB should not be affiliated with OHSU. Members may not be directly involved in the clinical trial design, implementation, or outcome evaluation of the clinical trial under their review. While these DSMB members should not be involved in any way with this specific clinical trial, the health-care professionals chosen should be selected with their expertise in the field of oncology under clinical trial in mind. Potential conflict of interest should be assessed for all members of the DSMB to ensure their objectivity during their service as a board member. Voting members of the DSMB may include physicians, statisticians, other scientists, and lay representatives selected based on their experience, reputation for objectivity, absence of conflicts of interest (and the appearance of same), and knowledge of clinical trial methodology.

⁴ NCI Policy for Data and Safety Monitoring of Clinical Clinical trials
<http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm>

The clinical trial specific DSMB shall work in cooperation with the Knight CRRC, DSMC and OHSU IRB, but will not replace any of those committees in the oversight of the clinical trial. The DSMB reports to the clinical trial principal investigator, the Knight CRRC and OHSU IRB.

Each DSMB should have a charter that outlines its data and safety monitoring plan for the specific clinical trial, including membership, what data will be reviewed and at what frequency, plans for any interim analyses and implementation of stopping rules.

The DSMB meetings should occur at least annually based on the needs of the specific clinical trial; meeting minutes are maintained. DSMB recommendations should be based on results for the clinical trials being monitored as well as other relevant data made available to the board. Reports of the DSMB should be submitted to the OHSU IRB and the Knight DSMC. The principal investigator is responsible for the submission of auditing report to the DSMB in the event that significant findings are noted.

QUALITY ASSURANCE AUDITING

The KCTO is responsible for conducting quality assurance audits of Knight Cancer Institute approved clinical trials that have no or limited safety/quality oversight by an external party. The purpose of a quality assurance audit is to ensure compliance to the requirements of the OHSU IRB-approved protocol, appropriate protections of the clinical trial participants, accuracy and completeness of clinical trial data, safety reporting requirements, and clinical trial drug management. Compliance with all federal regulations, NCI policies, and institutional requirements for the protection of human subjects are assessed. In addition, the audit provides an opportunity for education to the research staff regarding identified issues and assists departments in designing appropriate ways to correct deficiencies and strengthen research practices.

Audits are conducted by the KCTO auditing group under the authority of the Knight DSMC. The auditing team members will be knowledgeable of the protocol to be reviewed, audit procedures, clinical trials methodology and Knight Cancer Institute, other applicable OHSU policies and state and federal regulations. The auditing team members will not be directly involved in the conduct of the clinical trial.

Sponsor: Local, Investigator Initiated Clinical trials

Audits of Knight Cancer Institute investigator-initiated clinical trials (IITs) and NCI or NIH sponsored clinical trials are conducted on a yearly basis. Clinical trials with potentially higher risks, vulnerable populations or high accruals may be audited more frequently as specified in the DSMP for those clinical trials. If a clinical trial is audited by NCI or any other monitoring entity, the investigator should provide the audit findings to the Knight DSMC and IRB in a report form or in a summary based on the findings communicated during the audit.

External sites participating in a multi-center clinical trial sponsored by an OHSU investigator with their own DSMP must adhere to that plan by monitoring and auditing the clinical trial at their site. All monitoring and audit reports should be sent to Knight DSMC through the KCTO auditing group. The KCTO may conduct audits in addition to those conducted by the local site or may arrange to attend and observe any monitoring or audit of the clinical trial performed by the local site.

Sponsor: NCI Cooperative Groups

Each cooperative group maintains its own program of clinical trial monitoring and audits. Copies of the monitor and audit reports should be requested of the monitoring or auditing party and if obtained, a copy should be sent to the Knight DSMC through the Knight auditing group, and to the IRB as part of the continuing review process. The Knight auditing group may conduct audits in addition to those conducted by the cooperative group or may arrange to attend and observe any monitoring or audit visit conducted by the cooperative group.

Sponsor: Industry

Monitoring and auditing of industry-sponsored clinical trials are conducted by the Sponsor or its agent. Copies of the monitoring and audit reports should be requested of the monitoring or auditing party and if obtained, a copy should be sent to the Knight DSMC through the Knight auditing group, and the IRB as part of the continuing review process. If a report is not accessible, the investigator should provide any findings to the Knight DSMC in a summary based on the findings communicated during the audit. The Knight auditing group may conduct audits in addition to those conducted by the Sponsor or may arrange to attend and observe any monitoring or audit visit by the Sponsor.

If a clinical trial is to be inspected by the FDA or any other regulatory agency, the principal investigator or clinical trial coordinator will notify the Knight auditing group and will forward a copy of the summary letter and follow-up correspondence to the Knight DSMC.

Types of Audits

The audit program is divided into three categories: routine audits, targeted audits, and focused audits.

- Routine audits involve the selection of a clinical trial from a list of all ongoing clinical trials at the Knight Cancer Institute. A clinical trial selected for a routine audit typically has no known areas of concern.
- Targeted audits are conducted on a clinical trial with a known or suspected deficiency. Targeted audits may be performed in response to reports made to KCTO or by KCTO, at the request of the Knight DSMC, FDA, Office of Research Integrity, NCI, IRB, or a clinical trial's sponsor. Factors that might trigger a targeted audit include, but are not limited to, suspected inadequacies in clinical trial management, large numbers of serious adverse events, an excessive number of protocol deviations, inexperienced clinical trial personnel, late submissions of IRB continuing review information, and/or the IRB finding of serious and continuing non-compliance regarding a specific protocol.
- Focused audits typically review only specific audit categories (e.g., informed consent, eligibility, or toxicity). They are often initiated based on a known concern but may be conducted on a routine basis as an efficient mechanism to evaluate a large number of clinical trials. An example of a focused audit would be one assessing eligibility criteria for patients enrolled on a clinical trial with an unexpectedly high accrual rate.

Audit Conduct

An audit includes the review and evaluation of conformance to IRB, informed consent, protocol and regulatory requirements, drug accountability, clinical trial data and patient records. A minimum number of cases equivalent to 20 percent of the patients put on clinical trial since the last audit or at least five, whichever is the greater number of cases, will be audited. Source documentation shall be reviewed for independent verification of clinical trial data. Clinical trial conduct will be evaluated based on protocol compliance with the clinical trial schedule, regulatory requirements, and guidelines for Good Clinical Practice (GCP).

Specific aspects that are reviewed in detail, depending on the type of audit, include:

- Source documents
- Activation/Continuing Review Information
- Informed Consent Document and process
- Eligibility
- Protocol Compliance
- Treatment Administration
- Disease Outcome/Response
- Toxicity
- General Data Quality
- Accountability of Investigational Agents

A variance from the IRB- approved protocol that does not have a significant effect on the participant's rights, safety, welfare, and/or the integrity of the data is called a minor deficiency. Minor deficiencies may be caused by the action of the participant, the investigator, or the research staff (e.g. missed appointment due to transportation problem).

A major deficiency is defined as a variance from the IRB- approved protocol without prior approval of the sponsor and/or IRB that have a potential to have significant effect on the participant's rights, safety, welfare, and/or the integrity of the data and may cause an unanticipated problem to the patient or others. Major deficiencies may also significantly alter the clinical effectiveness of the treatment or the evaluation of its toxicity.

Audit findings

At the conclusion of the audit, the Knight auditing team conducts an exit meeting with the investigator and research staff where the preliminary findings and any recommendations from the audit are discussed. The principal investigator provides a response to each of the findings cited during the audit and when appropriate, a corrective action plan developed. The Knight auditing team subsequently completes a final written report including the principal investigator's responses to the findings and submits to the Knight DSMC for review.

Audits will be evaluated relative to the following definitions.

Acceptable	<ul style="list-style-type: none"> • Few minor deficiencies • Major deficiencies addressed/corrected prior to the audit
Acceptable, needs follow up	<ul style="list-style-type: none"> • Multiple minor deficiencies • Major deficiencies <u>not</u> corrected prior to the audit
Unacceptable	<ul style="list-style-type: none"> • Multiple major deficiencies • Single flagrant discrepancy • Multiple, recurrent minor deficiencies

If necessary, the committee identifies additional audit follow-up measures beyond those already identified during the interactions between the principal investigator and Knight auditing team. The measures are intended to be constructive and educational. Dependent on the gravity of the findings, the actions might include the conduct of a follow-up audit, education, closure of clinical trial enrollment or suspension of research privileges. If the audit findings identify issues related to subject welfare or scientific integrity, the information will be provided to the Associate Director of Clinical Research. Depending on the gravity of the audit findings, an ad-hoc discussion with Associate Director of Clinical Research, Knight CRRC, DSMC, and OHSU IRB representation may occur.

At the completion of the audit process, a final letter will be sent to the principal investigator summarizing the results. Audit results falling into the category of unacceptable will specify required actions and follow up. Investigators shall submit unacceptable audit findings to the IRB upon receipt of the report. All other audit reports shall be submitted to the IRB by the investigator as part of the continuing review process. If audit findings require submission of a UP or protocol deviation to the IRB, a copy of the audit report should be appended to the submission to the IRB. All records of the audit will be kept on file with the KCTO.

It is the responsibility of the Associate Director of Clinical Research to report any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial to the NCI grant program director responsible for the grant⁵.

Please refer to the Knight Cancer Institute Clinical Research Audit Plan for additional detail on the elements of the audit and the process for audit planning, conduct and follow-up.

ADVERSE EVENT AND UNANTICIPATED PROBLEM REPORTING

OHSU Knight Cancer Institute investigators and affiliate investigators follow local IRB standards, federal regulations and NCI/NIH guidelines in the reporting of adverse events (AEs) and unanticipated problems (Ups). AE and UP reporting procedures are detailed in each protocol and depend upon the type of clinical trial, the type and severity of adverse event, the clinical trial sponsor and Investigational New Drug (IND) status. For clinical trials where OHSU

⁵ Notice To NIH Grantees/Contractors Regarding Letters Or Notices From The Food And Drug Administration (FDA) <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html>

is the coordinating center, centralized adverse event reporting mechanism and requirements will be instituted. These reporting requirements are summarized below and in Table 2.

- Adverse events may be reported by the principal investigator to one or more of the following parties:
 - Knight DSMC: component of the protocol data review process (quarterly for Phase I clinical trials and twice-yearly for Phase II and III clinical trials). The extent of adverse event review by the Knight DSMC is predicated on the complexity of the protocol and any safety signals noted in the present clinical trial or other clinical trials evaluating the same agent(s). Minimally events of Grade 3, 4 and 5 will be reviewed.
 - NCI Cancer Therapy Evaluation Program (CTEP): clinical trials conducted under a CTEP sponsorship and/or by a NCI cooperative group in accordance with protocol requirements
 - OHSU IRB: if event is an UP
- Serious adverse events are reported by the principal investigator to one or more of the following parties:
 - Knight DSMC: component of the protocol data review process (quarterly for Phase I clinical trials and twice-yearly for Phase II and III clinical trials)
 - NCI CTEP: clinical trials conducted under a CTEP sponsorship and/or by a NCI cooperative group
 - OHSU IRB: If event is an UP, it is reported electronically via the eIRB and the OHSU Annual Event Summary Form⁶ is to be submitted at continuing review, all in accordance with the OHSU IRB Policy and Procedure entitled Reporting Unanticipated Problems and Adverse Events⁷.
 - FDA:
 - Clinical trials conducted under IND held by OHSU investigator in accordance with 21 CFR Part 312.32 Expedited Safety Reporting Requirements for Human Drug and Biological Products⁸
 - Clinical trials conducted with a commercially available agent/device (no IND involved), reported through FDA Form 3500 (MedWatch)⁹

⁶ OHSU Annual Event Summary Form <http://www.ohsu.edu/xd/about/services/integrity/policies/irb-forms.cfm>; <https://irb.ohsu.edu/irb>.

⁷ OHSU IRB Policy and Procedure entitled Reporting Unanticipated Problems and Adverse Events <http://www.ohsu.edu/xd/about/services/integrity/policies/upload/Unanticipated-Problems-Regulatory-Sheet.pdf>

⁸ 21 CFR 312.32 IND Safety Reports <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32>

⁹ FDA Form 3500 (MedWatch) Instructions and Form <http://www.fda.gov/Safety/MedWatch/default.htm>

- NIH Office for Biotechnology Activities: If a clinical trial involves recombinant DNA molecules (gene transfer), NIH Guidelines for Research Involving Recombinant DNA Molecules will be followed¹⁰.
- Unanticipated problems are reported to the following parties:
 - Knight DSMC: component of the protocol data review process (quarterly for Phase I clinical trials and twice-yearly for Phase II and III clinical trials)
 - OHSU IRB

Table 2: Potential Adverse Event and Unanticipated Problem Reporting Requirements
(see detail above for caveats for reporting requirements)

Review committee or Agency	Adverse Event	Serious Adverse Event	Unanticipated Problem
Knight DSMC	X	X	X
OHSU IRB			X
NCI CTEP	X	X	
FDA		X	
NIH Office for Biotechnology Activities		X	

¹⁰ NIH Guidelines for Research Involving Recombinant DNA Molecules
http://oba.od.nih.gov/rdna/nih_guidelines_oba.html

**Appendix A: Knight Cancer Institute Clinical Trial Data and Safety Monitoring
Organizational Chart**

