Stanford University Cancer Center

Institutional Data and Safety Monitoring Plan

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Abbreviations

CCTO	Cancer Clinical Trials Office
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CTEP	Cancer Therapy Evaluation Program
DHHS	Department of Health and Human Services
DM	Data Manager
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCRC	General Clinical Research Center
IDB	Investigational Drug Branch
IND	Investigational New Drug
IRB	Institutional Review Board
NCI	National Cancer Institute
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities
PD	Protocol Director
PI	Principal Investigator
PRMS	Protocol Review and Monitoring System
PHS	Public Health Service
SAE	Serious Adverse Events
SRC	Scientific Review Committee

Overview

Data and safety monitoring is intended to oversee all aspects of data monitoring, verify data validity and integrity, and ensure the safety of participants in all clinical trials, including institutionally sponsored, investigator initiated trials, and those trials without external monitoring that are active at Stanford University Cancer Center and Lucile Packard Children's Hospital. All clinical trials require monitoring commensurate with the degree of risk involved in study subject participation, as well as the size and complexity of the study. The Principal Investigator and the organization's infrastructure assume the responsibility of the ongoing monitoring process. In some circumstances, a contracted research organization (CRO) may be used to aid the monitoring process.

This document details the Stanford University Cancer Center's Data and Safety Monitoring Plan. This plan outlines the general process for data and safety monitoring, including institutional oversight and review procedures important to ensure and document compliance. This plan is designed to ensure the safety of participants, the validity of data, and the appropriate termination of studies in the event that undue risks have been uncovered, or it appears that trials cannot be conducted successfully. The institutional plan covers all clinical trials involving patients with cancer. The plan applies to all phases of clinical therapeutic intervention, including behavioral clinical trials and diagnostic trials that involve medical decision making that impacts the treatment of cancer patients. Particular attention is paid to monitoring investigator-initiated clinical trials, especially those for which there is no independent outside monitoring program.

The plan complies with the NIH/NCI guidelines published as *NIH Policy for Data and Safety Monitoring* as of June 10, 1998, *Policy of the NCI for Data and Safety Monitoring of Clinical Trials* as of June 22, 1999, *Further Guidelines on a Data and Safety Monitoring Plan for Phase I and II Trials* from the NIH on June 5, 2000, *Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the NCI* as of April 2001, and The Cancer Centers Branch of the National Cancer Institute Parts I and II: Policies and Guidelines Relating to the Cancer Center Support Grant, dated September 2004. This document summarizes policies regarding protocol approval, safety procedures and reporting, and institutional administrative oversight.

Data and Safety Monitoring at the Stanford University Cancer Center

All new cancer-related clinical trial applications proposing involvement of Stanford subjects (treatment and non-treatment, regardless of sponsorship) must be reviewed and approved by the Stanford University Cancer Center's Scientific Review Committee (SRC) as well as the Stanford University Institutional Review Board (IRB). This document contains the guidelines for the data and safety monitoring of those clinical trials once approved by the SRC and IRB. The Stanford University Cancer Center's Protocol Review and Monitoring System (PRMS) Data and Safety Monitoring Committee (DSMC) is charged with conducting clinical trial monitoring. This committee reports to the Director of the Protocol Review and Monitoring System. The Director of the PRMS reports to the Director of the Stanford University Cancer Center. See Appendix I for a detailed flow diagram of the steps involved in moving a clinical trial through these committees.

The DSMC is the Data and Safety Monitoring Board (DSMB) for the Stanford University Cancer Center. The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials at the Stanford University Cancer Center. The committee meets monthly to review the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board. If a study is already being monitored by a data and safety monitoring committee formed by a national cooperative group, a pharmaceutical sponsor, or a study-specific committee for a Phase III trial, the DSMC does not actively monitor the study. In this case, the DSMC oversees the process of adverse event reporting to ensure that the requirements are met, and performs an annual review to judge the acceptability of continued research based upon the risk/benefit ratio, clinical relevance, and institutional priorities. The DSMC has the authority to require

amendments and to recommend suspension or termination of any research activities that fall within its jurisdiction. The DSMC can institute any other appropriate conditions needed for subject safety.

The remainder of this document provides details about the DSMC and its level of monitoring, standard monitoring procedures, committee actions, reports, and communications. The appendices of this document provide the committee membership list, sample monitoring forms, detailed procedures, and information about how adverse events are to be reported.

Applicability

It is recognized that clinical trials sponsored by NCI cooperative groups and industry are continually audited for compliance and monitored for progress. However, institutional clinical trials without outside sponsorship are not audited and are the focus of the monitoring system described here.

Definition of a Clinical Trial

A *clinical trial* is defined here as a prospective study involving human subjects designed to answer specific questions about the effect or impact of particular biomedical research or behavioral interventions; these interventions may include drugs, treatments, procedures, devices, or behavioral or nutritional strategies. Participants in clinical trials may be patients with cancer or people without a diagnosis of cancer, but at risk for developing cancer in the future.

With regard to *diagnostic research* employing tissue and/or body fluids, a study is considered to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. This information may impact some aspect of the study's outcome, and the assessment of this impact may be a key goal of the trial. In contrast, tissue and body fluid studies that do not use this information in any manner that can affect the outcome of study subjects are not clinical trials and are NOT covered by this policy (unless gathering the tissue or body fluids itself imposes some risk on study subjects).

With regard to *diagnostic research* utilizing molecular or imaging diagnostics, a study is considered to be a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. This information may impact some aspect of the study's outcome, and the assessment of this impact may be a key goal of the trial. In contrast, studies that do not use this information in any manner that can affect the outcome of study subjects are not clinical trials and are NOT covered by this policy (unless performing the diagnostic test itself imposes some risk on study subjects). These are studies in which the only objective is gathering data on the characteristics of a new diagnostic approach.

Behavioral clinical trials test interventions aimed at eliminating or reducing human activities associated with enhanced cancer risk (e.g., tobacco use, poor nutrition, and sun exposure), or eliminating or reducing morbidity associated with cancer screening, diagnosis, and treatment.

Definition of an Investigator-Initiated Clinical Trial

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

NIH-supported, large-scale, multi-site Phase III therapeutic intervention clinical trials involving significant risk

are internally reviewed on an annual basis. Independent Data and Safety Monitoring Boards (DSMBs) for such studies are established by the Principal Investigator and supported through the funding agency. NIH-supported Phase III clinical trials that involve only low risk (i.e., behavioral and nutritional research) are reviewed on a case-by-case basis, as their sample size may be too large to be practically monitored by this system. In some cases, these studies require an independent DSMB.

Data and Safety Monitoring Committee (DSMC)

The Stanford University Cancer Center's Data and Safety Monitoring Committee (DSMC) is responsible for ensuring that data generated by Cancer Center investigators is of high quality, reliable, and verifiable. The mission of the DSMC is to:

- Develop quality assurance procedures to monitor the on-going safety of study subjects and the overall conduct and progress of investigator-initiated clinical trials
- Ensure adherence to these quality assurance procedures and Good Clinical Practice (GCP) guidelines by conducting regular monitoring reviews

Routine monitoring is performed to ensure that:

- Participants are safe.
- Data are valid.
- Eligibility and evaluability rates do not fall below minimum standards.
- Risks are not excessive.
- Adverse events are identified and reported to the appropriate agencies, regulatory bodies, and committees.

Membership

The Directors of the Stanford University Cancer Center and the PRMS appoint the DSMC Chair. The DSMC Chair, in consultation with the Director of the PRMS, appoints members to the DSMC. There are a minimum of seven members on the committee including at least four physicians, one oncology nurse, one oncology data manager, and one biostatistician who may serve for an indefinite period. Members are selected to provide a diverse group with expertise in several specialty areas such as medical oncology, radiation oncology, hematology, bone marrow transplantation, and pediatric oncology. When additional expertise is required, the Chair may appoint additional members on an ad hoc basis. Six or more members constitute a quorum.

The NCI is provided with a current committee membership list at the time of the initial submission of the grant application. The membership list is then updated regularly and submitted to the NCI along with the annual report.

Appendix II lists the current DSMC membership.

The Chair facilitates each meeting and guides discussion to formalize action on each study that is reviewed. Meeting agendas include annual reviews, results of monitoring sessions, and reports of serious adverse events (SAEs). The Chair ensures that all protocols monitored by the DSMC receive timely monitoring, that monitors are assigned, monitoring results and reported SAEs are adequately discussed, action taken, and that feedback is provided to the Principal Investigator within one week of committee action. The Vice Chair executes the responsibilities of the Chair when the Chair is unavailable or as delegated by the Chair.

The Monitoring Team

The Monitoring Team for a particular study consists of at least one faculty member along with the PRMS Coordinator from the DSMC and, when needed, additional volunteers with expertise in the specialty area under review. The DSMC Chair periodically participates in Monitoring Team meetings and gives advice and direction to the team as necessary, particularly with respect to reviewing the complexity and level of risk of the study under review.

Conflict of Interest

Stanford faculty and research staff volunteer as DSMC Monitoring Team members. There is potential for conflict of interest to exist if Monitoring Team members have an indirect or direct relationship with the study under review. An example of an indirect relationship is a Monitoring Team member who participates in any administrative activity involving study conduct, such as preparing annual IRB reports or conducting any laboratory procedures, whereas an example of a direct relationship is a team member who participates in a clinical role as the Principal Investigator, Sub-Investigator, Research Nurse, Clinical Research Associate (CRA), Data Manager (DM), or a statistician who is involved in data analysis. Further, any physician or research staff member who receives any funding from the study grant has a potential for a conflict of interest. No one who has an indirect or direct relationship with the study under review is allowed to serve on a Monitoring Team. No one is allowed to be present during DSMC deliberations, or cast a vote if they are a research team member of the study being reviewed or if they have a conflict of interest due to a relationship with the sponsor, intellectual property ownership with study investigators, or personal financial investments related to the study or study sponsor.

Meetings

The DSMC meets once a month. The Chair may convene additional meetings when deemed necessary.

Each meeting includes a review of safety reports for attribution and trending; review of protocol deviations; review of monitoring results and study status; and determination of communications to Principal Investigators, Study Coordinators, SRC, CCTO, IRB, and GCRC.

Administrative Coordination

The PRMS Coordinator of the Protocol Review and Monitoring System provides administrative support to the DSMC. This includes database management, report generation, meeting coordination, and minutes preparation. Minutes reflect members present, substantive issues discussed, voting results, and members abstaining due to conflict of interest. The PRMS Coordinator is responsible for ensuring that follow-up activities occur in a timely manner. All records of committee activities are maintained in the PRMS office by the PRMS Coordinator.

Determining the Level of Risk of a Study

Each investigator-initiated and/or NCI-funded trial undergoes scientific review by the SRC, in part, to ensure that procedures are in place to ensure the safety of subjects depending on the degree of risk of the study. In collaboration with the SRC Chair, the DSMC Chair assigns a category of risk to every investigator-initiated study. This risk category determines the level of monitoring required. Factors taken into consideration include:

- An adequate biostatistical design and procedures to collect adequate data and perform appropriate data analyses in order to ensure the validity and integrity of the data
- Expected duration of the study based on a realistic enrollment rate
- Data management systems to ensure eligibility of subjects and adequacy of data collection procedures.

Multiple-site studies must include an operational plan that describes the overall operational and monitoring plans.

- Serious adverse event reporting procedures that are appropriate

Assignment of Risk

The purpose of assigning a level of risk (low, moderate, or high) to an investigator-initiated or NCI-sponsored trial is to ensure that data and safety monitoring activities are appropriate. In order to make a decision, the committee reviews these criteria:

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

Levels of Risk

High Risk

Studies assigned to the high-risk category include any investigator-initiated Phase I, II, or III trials, investigator-initiated multi-center trials, any research involving recombinant DNA molecules (gene transfer), and all investigator-initiated IND trials. For example, a Phase I trial of a new drug or agent frequently involves a relatively high risk to a small number of participants. These clinical trials involve the first use of the drug in humans, so the investigator may have the only relevant knowledge regarding the use of such new drugs.

Moderate Risk

Studies assigned to the moderate-risk category include most investigator-initiated Phase II trials and Phase I trials using FDA-approved, commercially available compounds. For example, a typical Phase II trial follows a Phase I study and there is usually more detailed information regarding the risks, benefits, and necessary monitoring procedures. However, more participants are involved and the disease process may confound the toxicity profile. In this case, the DSMC may decide that the study requires monitoring similar to that of a Phase I trial, or choose to supplement the actual Monitoring Team with experts in the study indication who can assist in interpreting the data to ensure subject safety.

Low Risk

Studies assigned to the low-risk category include cooperative group studies (ECOG, SWOG, NSABP, COG, and GOG) because they already have independent data monitoring boards in place, as well as most non-therapeutic trials. For example, a Phase III trial often compares a new treatment to standard treatment or no treatment. Treatment allocations may be randomly assigned; and the data may also be masked. Studies such as these require many participants who are monitored long after study completion. While the short-term risk is usually slight, the long-term effects of an investigational agent, or the achievement of significant safety or efficacy differences between the groups needs to be addressed on an on-going basis. In this case, the DSMC may require a separate DSMB composed of medical experts who perform safety and data monitoring and make appropriate recommendations regarding safety to the DSMC.

Level of Monitoring According to Level of Risk

The study is assigned a monitoring milestone or a review date, depending on the level of risk determined as above. The milestone is also based upon a specific accrual target.

Monitoring and Review

Initial Monitoring Review

The **minimum level** of monitoring required for investigator-initiated treatment studies is a full monitoring review on an annual basis (see Appendix III). Repeated monitoring may be required based on the findings of the initial review. If the DSMC rates the initial review as satisfactory, the study is subsequently reviewed each year prior to the time of the annual IRB renewal.

Re-monitoring

Studies that received a rating less than satisfactory during the initial monitoring review are reviewed again by the DSMC on a case-by-case basis. Any follow-up recommendations such as a corrective action plan or re-monitoring are based upon the results of the monitoring review. For example, findings such as the type and degree of protocol deviations or violations, unreported serious adverse events, and investigational drug medication errors may warrant further review. A corrective action plan requires a prompt response by the Principal Investigator. Once the DSMC determines that the corrective action plan is adequate to ensure subject safety, re-monitoring is determined by the rate of subject accrual.

Continuing Review

Continuing study reviews include a progress report (see Protocol Monitoring Form Page 1, Appendix IV) completed by the DSMC staff in cooperation with the study's research staff. Continuing reviews do not require full monitoring by a team, and occur annually at a minimum. The DSMC reviews the study's progress report and makes an assessment as to whether any additional monitoring is warranted. For example, any concerns regarding subject outcomes, such as the frequency and severity of serious adverse events, may require more frequent monitoring. The subject registration process is verified during the continuing review. Failure to register subjects in the Oncore database is considered a major deficiency.

When directed by the DSMC, a Monitoring Team reviews the study using the same procedure as used for a full monitoring review and reports back to the DSMC. Based upon these results, the DSMC determines if any additional action is required.

Data and safety monitoring activities and continuing study reviews take place until all subjects have completed any protocol-related activities and are beyond the time point at which any study-related adverse events may occur.

Data and Safety Monitoring Procedures

Subject Registration

The Cancer Clinical Trials Office (CCTO) is responsible for tracking and reporting about all subjects who enroll in cancer-related trials. To accomplish this, all subjects enrolled in cancer studies must be registered in the Oncore database. Investigators, research nurses, and study coordinators are given two options for conveying subject registration information to the CCTO. A member of the study team can enter the subject information directly into Oncore or the information can be provided to the CCTO. A subject registration form (Appendix

V) is available. The completeness of subject registration information is verified during the review of each study.

Initial and Continuing Review of IRB Compliance

All cancer-related clinical trials, regardless of sponsorship, must be reviewed and approved by the Scientific Review Committee (SRC) as well as the Stanford IRB before the study is opened to accrual. To ensure that subjects are not enrolled in studies prior to final IRB and SRC approval, a checkpoint is built into the Oncore database that rejects registration of subjects if the date of final approvals has not been encoded or has lapsed. If an attempt is made to register a subject before evidence of final IRB and SRC approval exists, the CCTO notifies the PI, the SRC, and the IRB. At the time of annual renewal, the IRB application is submitted in parallel to the SRC for review. The subject accrual data reported in the renewal application is verified against the subject registration data in the Oncore database. SRC approval of the renewal application is not granted until both data sets are consistent.

Scientific Progress

All investigator-initiated clinical trials are monitored annually for scientific progress and GCP compliance. During the annual review, the Protocol Monitoring Form is completed (Appendix IV, Page 1). The DSMC reviews each annual report and makes a recommendation regarding continuation. The results of this review are shared with the SRC. The committee regards the scientific review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated.

Each investigator-initiated clinical trial represents a unique set of factors affecting study activation, subject accrual, and study conduct. For example, during the review process, the committee reviews study data including evaluations of response and toxicity, as well as an interim statistical analysis, if appropriate. In addition, when the Principal Investigator of a multi-center study is a Stanford physician, all subjects must be registered in the Oncore database to enable the DSMC to judge the aggregate accrual and appropriateness of the application of stopping rules for the study. At the next Monitoring Team review, the status of subject accrual is addressed to ensure that data for all participating centers is captured.

Monitoring Procedures

Prior to the monitoring of a study, all studies should have a monitoring plan approved by the SRC. The DSMC then determines when to monitor the study based upon the level of risk and accrual (as above). The Monitoring Team Coordinator manages the logistics associated with monitoring review sessions. A typical timeline of activities leading up to the monitoring session is detailed in Appendix VI.

Case Selection

Once a clinical trial is identified for monitoring, the Monitoring Team Coordinator arranges for a random selection of cases to monitor from among all subjects registered in the database. If subjects of Stanford affiliate sites are enrolled, cases from those sites are randomly selected for review as well. Copies of these case materials are to be sent by the affiliate to Stanford for review by the DSMC Monitoring Team.

Notification

The Principal Investigator and Study Coordinators are notified in advance of a scheduled monitoring session in which subjects have been randomly selected for review by the PRMS Coordinator of the PRMS. The Monitoring Team Coordinator contacts the study team to arrange for a mutually agreed upon time for the monitoring session.

The investigator and the research staff are responsible for gathering all of the materials germane to the review

including medical records, case reports forms, and any other research records requested. If affiliate centers are enrolling subjects, materials needed for the review from the outside centers must be provided to the Monitoring Team.

Specific information requested for the monitoring session includes:

- Copies of serious adverse event reports, follow-up reports, and outcome reports
- Current disease, demographic data, and on/off study status of subjects
- Type and grade (if applicable) of adverse events for all subjects enrolled; grade 3 and 4 only
- Electronic copy of the protocol (if not in *Oncore*)
- Expected and actual numbers of subjects accrued to date
- Dates that subjects enrolled in study
- Description of any changes to the study design (amendments, updates to Investigator Brochure)
- Exceptions in eligibility or treatment

Monitoring Session Preparation

The Monitoring Team Coordinator reviews the protocol, any serious adverse event (SAE) reports, and regulatory documentation prior to the monitoring session and completes the Monitoring Question List - Regulatory Form (Appendix VIII). Other members of the team also review the study protocol prior to the monitoring session.

Monitoring Session Implementation

The Monitoring Team uses the primary medical record as the central document. The source documents are checked to ensure that subjects were not treated on the clinical trial prior to final SRC or IRB approval. The following areas are examined and documented on the Protocol Monitoring Form (see Appendix IV):

- Informed consent was properly obtained.
- Any required pre-study tests and procedures were obtained within the designated pre-treatment time interval.
- Eligibility criteria were accurately met.
- Adherence to treatment plan is documented including administered drug doses and any drug reductions and/or treatment delays if indicated.
- Accuracy, adequacy, completeness, and timeliness of data collection and submission.
- Appropriate and timely reporting of adverse events (AEs) and serious adverse events (SAEs) to the IRB and GCRC, and/or external agencies, relevant committees, or sponsors.
- Adherence to subject follow-up requirements.

Consistency of data in the research record or Case Report Form (CRF) is verified with data in the medical record.

Verification of Adverse Event (AE) Reporting

All new clinical trials are required to contain a description of procedures for adverse event (AE) reporting at the time they are reviewed by the SRC. Depending on the type of intervention proposed, the clinical trial must contain a grading system for adverse events (i.e., NCI Common Toxicity Criteria), reference the reporting forms to be used (investigational vs. non-investigational drug reporting), and describe oversight by the investigator for

grading and attribution of AE's to the study intervention. The investigator is responsible for submitting serious adverse event reports to the IRB, sponsor, and/or appropriate agencies described in the protocol (Appendix III). These may include the pharmaceutical sponsor, NCI, NIH, and/or FDA. SAE reports are also submitted to the CCTO so that they can be tracked in the Oncore database, and reviewed by the DSMC. Information on reporting requirements is periodically distributed to all clinical investigators. If any SAEs are identified during a monitoring session, the responsible Principal Investigator must promptly report the SAE to the Stanford IRB, sponsor, and/or other appropriate agencies.

Ratings and Recommendations

Following the Monitoring Team session, the Monitoring Team Coordinator together with the Monitoring Team completes the Protocol Monitoring Form (Appendix IV) that lists the previous DSMC review history (if any) and describes the findings of the Monitoring Team. The completed Protocol Monitoring Form is distributed to the full DSMC for review. During the next full committee meeting, an overall rating is assigned to the study (full approval, conditional approval, suspension, or closure) that is a composite of subject accrual, overall study conduct, and the findings of the monitoring session. For example, if a study has no deficiencies in study conduct, but is lagging in accrual or violating any stopping rules, an unsatisfactory or marginal rating may apply depending upon the degree of violation.

In rating the conduct of the study, the DSMC categorizes deviations as **Major** or **Minor**. The DSMC exercises reasonable judgment in determining if a deviation is considered major or minor, as follows.

Major deviations are those variances from clinical trial-specified criteria or procedures that make the resulting data questionable. Examples of these include subject ineligibility, failure to document informed consent or to obtain informed consent prior to the initiation of treatment or study-related screening procedures/tests, failure to comply with IRB approval and/or re-approval guidelines, and protocol deviations such as substantial alteration or modifications of doses outside the study parameters, and/or poor data quality such as errors in data entry, not capturing toxicities and dose limiting toxicities, and failure to report serious adverse events. The subject registration process is also verified at the time of the monitoring review session. Failure to register subjects with the CCTO is considered a major deficiency.

Minor deviations are those that do not affect the outcome or interpretation of the study and are not described above as major deviations. For example, a hematology value that is a minor variance from the study specifications is a minor deviation whereas a MUGA result that is a significant variance from a study specification of cardiac function is considered a major deviation. The DSMC categorizes deviations as major or minor on a case-by-case basis. An unacceptable frequency of minor deviations is treated as a major deviation.

Overall Ratings

The following guideline is used to determine the rating:

Overall Rating	Major Deviations	Minor Deviations
Outstanding	None	0-3
Satisfactory	None	4-6
Minor Deficiencies	1	4-6
Major Deficiencies	2 or More	7 or More

Actions/Recommendations Based on Rating

The DSMC determines the overall rating based upon the results of the monitoring session and in accordance

with the above guidelines. The committee may make additional recommendations to address minor deviations as well as determine future monitoring plans. The following table summarizes some of the common ratings or issues identified, and actions taken:

Rating or Issue	DSMC Subsequent Monitoring Plans
Outstanding	Annual review is conducted to document accrual and SAE/AE reporting.
Less than Satisfactory	Study is judged individually and follow-up actions are taken in accordance with the type and degree of the deviations and/or violations. Depending on the nature of the findings and the investigator's response, early re-review is decided upon on a case-by-case basis at the discretion of the DSMC. For example, if the investigator proposes a corrective action plan, this may warrant an early re-review to determine its impact.
Under Accrual Noted	Memo sent to the PI; accrual reviewed at next monitoring session or at time of annual review.
Eligibility Issues	When eligibility issues are encountered. The eligibility of all subjects entered into the study to date is reviewed. Repeat Monitoring Team review conducted after a specified number of additional subjects are enrolled (usually 3). The purpose of the review is to verify that any eligibility issues have been resolved. The PI is notified of the issue(s) and the plan to re-monitor. The Oncore database is updated accordingly.

Once they have determined the rating, the committee votes on the following types of recommendations:

- **Full Approval:** Enrollment may continue; no outstanding questions regarding toxicity or accrual.
- **Conditional Approval:** Enrollment may continue conditional upon a satisfactory response by the Principal Investigator to the DSMC concerning study conduct, toxicities, and/or accrual.
- **Suspension:** Enrollment is immediately suspended pending Principal Investigator response to DSMC concerns regarding serious protocol deviations, toxicities, and/or accrual patterns.
- **Closure:** Study is closed due to unacceptable study conduct, toxicities, and/or accrual patterns.

The DSMC Chair conveys the DSMC decision to the study's Principal Investigator in writing. The PI also receives a copy of the Protocol Monitoring Form (Appendix IV). If the PI decides to appeal the DSMC decision, he/she may do so in writing. If the appeal is unsatisfactory, the PI may appeal to the PRMS Executive Committee. See Appendix II for PRMS Executive Committee Membership.

Recommendation of Suspension or Closure

The DSMC may decide to recommend conditional approval, suspension, or closure of the clinical trial depending on the significance of the following deviations:

1. Stopping rule violations
2. Serious IRB violations (such as treatment without approval) that result in an unacceptable monitoring rating
3. Two sequential unsatisfactory monitoring ratings

Recommending the suspension or termination of a clinical trial is carefully considered. Particular consideration is given to any corrective action(s) that were implemented by the Principal Investigator.

Reporting Data and Safety Monitoring Findings

Internal Reporting

When the DSMC recommends suspension or study closure, the Chair notifies the Director of the PRMS, the Chair of the SRC, the Associate Director Clinical Research Stanford University Cancer Center, the Principal Investigator, the GCRC if applicable, and the IRB by letter at the same time.

External Reporting

Any temporary or permanent suspension of an NIH- or NCI-sponsored clinical trial study is reported immediately to the NIH or the NCI. In addition, any suspension, either temporary or permanent, of a trial in which CTEP supplies the study drug is reported immediately to CTEP.

The agencies are notified as soon as the issues are resolved by the Principal Investigator and the trial is re-opened to accrual.

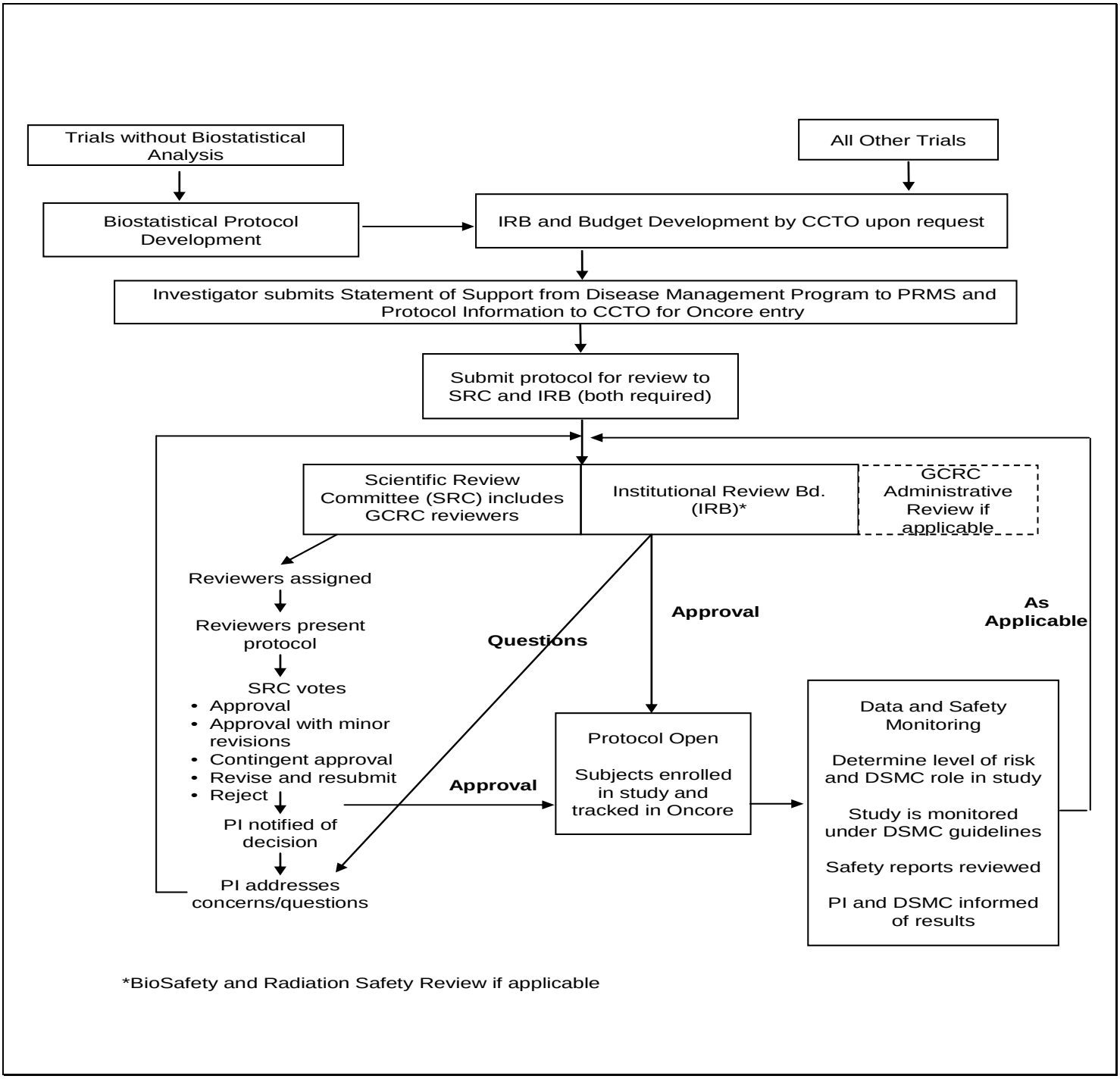
Confidentiality Procedures

No communication, either written or oral, of the deliberations or recommendations of the DSMC is allowed outside the DSMC except as provided for in this policy. It is also understood that industry studies are considered proprietary to the sponsor. Any outcome results are strictly confidential and must not be divulged to anyone who is not a member of the DSMC except as specified above.

Appendices

Appendix I: Diagram of Cancer Clinical Trials Review Process

A cancer clinical trial must go through several levels of review and approvals before it can be opened, subjects enrolled, and qualify for monitoring. This diagram shows the steps a trial goes through.



Appendix II: Committee Member Lists

Data and Safety Monitoring Committee Membership List

Susan Knox, M.D., Ph.D., Radiation Oncology, Chair

Sandhya Srinivas, M.D., Medical Oncology, Vice Chair

Karl Blume, M.D., Senior Cancer Research Program Advisor, Ex-Officio Member

Linda Boxer, M.D., Ph.D., Hematology

Steve Cavella, Compliance Coordinator

Mary Chen, R.N., Medical Oncology

Lee Doherty, Ed.M., Regulatory Specialist

Linda Elder, Research Coordinator

Ellie Guardino, M.D., Ph.D., Medical Oncology

Judith Hallagan, R.N., Pediatric Hematology/Oncology

Denise Johnson, M.D., Surgery

Bhagyashree Kelshikar, Study Coordinator

Tse Lai, Ph.D., Statistics

Ginna G. Laport, M.D., Bone Marrow Transplant

Nancy Mori, Study Coordinator

Sunil Reddy, M.D., Medical Oncology

D. Kathryn Tierney, R.N., PhD(c), Bone Marrow Transplant

Ben B. Varasteh, GCRC Lab Manager

Protocol Review and Monitoring System Executive Committee Membership List

Susan Knox, M.D., Ph.D., Faculty Director PRMS and DSMC Chair.

Miriam Bischoff, M.S., M.B.A., Facility Director PRMS and Cancer Clinical Trials Office

Karl Blume, M.D., Senior Cancer Research Program Advisor

Robert Carlson, M.D., Scientific Review Committee Chair

Beverly Mitchell, M.D., Deputy Director, Cancer Center

Stanley Schrier, MD, Scientific Review Committee Vice Chair

Sandhya Srinivas, M.D., DSMC Vice Chair

Appendix III: Summary of Types of Trials and Associated Monitoring Requirements

The phase of the individual trial directs the manner and degree of monitoring. This appendix describes the degree of oversight used for each phase of clinical trial. Listed under each study phase are procedures to follow for studies conducted under the various types of sponsors: NIH/NCI, industry, and investigator-initiated.

PHASE III STUDIES

A. NIH/NCI Sponsored Trials

National Cooperative Oncology Group Protocols

The Stanford University Cancer Center conducts clinical trials of the Eastern Oncology Group (ECOG), Southwest Oncology Group (SWOG), Children's Oncology Group (COG), National Surgical Adjuvant Breast/Colorectal Program (NSABP), and the Gynecologic Oncology Group (GOG).

Upon initial review of a Phase III cooperative group clinical trial, the Scientific Review Committee (SRC) verifies that a DSMB exists and is overseen by the study sponsor (cooperative group) or agency. If the DSMB oversight in a cooperative group protocol is not clear, the protocol is not activated until clarification is obtained.

Cooperative group trials are multi-institutional and use specific data management systems that closely monitor safety and efficacy data for each study by site and for the group as a whole. The Stanford University Cancer Center relies on established reporting mechanisms to monitor subjects on these studies, and does not require additional monitoring for these trials. However, all serious adverse events (SAEs) from these trials are required to be reported to the CCTO, DSMC, and the IRB.

Other NIH Grants

Other types of government grants may support large, randomized, Phase III trials. Any R01-funded Phase III study requires the utilization of a Data Safety and Monitoring Board (DSMB) to monitor adverse events and efficacy and to take action as necessary to protect participating subjects from unnecessary risks. Phase II NIH-funded trials conducted at the Stanford University Cancer Center utilize a study-specific, independent DSMB. This board oversees monitoring for trials which may be supported through various funding mechanisms of the NIH, including P01s, and also trials that are receiving sufficient CCSG support to be considered NCI-supported studies. For studies not initiated at Stanford, as in the case of cooperative group trials, the SRC verifies that a DSMB exists and is overseen by the study sponsor or agency. No further action regarding monitoring takes place on an institutional level, aside from serious adverse event reporting and the annual review of study progress conducted by the DSMC. If the DSMB oversight in such a protocol is not clear, the protocol is not activated until clarification is obtained. All study-specific DSMB reports are forwarded to the study PI, the Stanford University IRB, the CCTO, and the DSMC.

B. Industry-Sponsored or Industry-Supported Trials

All clinical trials initiated by pharmaceutical industry sponsors with the Stanford University Cancer Center as a participating site must have a data and safety monitoring plan in order for the trial to be approved by both the SRC and IRB. These protocol-specific plans adhere to industry and FDA-specified guidelines. The Scientific Review Committee verifies that a DSMB exists and is overseen by the study sponsor. Monitoring of serious adverse event reports continues on an institutional level. DSMB responsibilities are conducted by the sponsor, as ascertained in the protocol review. Local reporting for data and safety monitoring for industry-sponsored trials requires SAEs to be reported to the CCTO, DSMC, and IRB, using either industry-specified report formats or the FDA MEDWATCH SAE reporting form. Study progress is reviewed on an annual basis by the DSMC.

C. External Peer Review Trials

These therapeutic clinical trials often require more subjects than a single institution would be able to enroll,

which has led to the conduct of these studies in multiple institutions with collaborative agreements between investigators and institutions, outside of a formal cooperative group setting. Monitoring for these studies initiated at Stanford's Cancer Center is identical to monitoring for local, investigator-initiated trials (see section D).

For non-cooperative group, limited-institution Phase III studies without NCI/NIH monitoring, the PI at the lead institution is responsible for monitoring the study and establishing the use of a DSMB. Prior to activating the study at Stanford, upon initial review of the protocol, the SRC reviews and approves data and safety monitoring plans and verifies the existence of the specified external DSMB.

As noted previously, investigators must be aware of NIH policy *Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials* (NIH Guide for Grants and Contracts, June 11, 1999) and *NIH Policy on Data and Safety Monitoring* (NIH Guide for Grants and Contracts, June 10, 1998). These documents are relevant to multicenter, limited-institution trials.

D. Investigator-initiated Studies

Local, investigator-initiated studies, while including many studies with NIH sponsorship, are often reliant only upon local funding or pharmaceutical industry funding. These trials include studies that may receive partial or full external funding, and they require particular attention for local monitoring. These studies receive particularly high priority for local oversight.

Since randomized Phase III studies usually require large subject populations with lengthy subject follow-up, such trials are rarely implemented as local studies. Historically at Stanford, few exclusively local Phase III trials have been planned or conducted (and any such protocols were conducted prior to the NIH requirement for specific independent data and safety monitoring). These investigator-initiated Phase III trials (or similar randomized Phase II trials) in which the study PI is a Stanford University faculty or staff member, are monitored by a study-specific, independent DSMB.

The large number of subjects required for comparative randomized Phase III trials necessitates an emphasis on ensuring subject safety. Typically, such trials are conducted over a longer time frame than Phase I and II trials. With the likelihood of a large number of subjects included for longer exposure to investigational regimens, and with a longer period of subject recruitment, the potential for increased risk to subjects exists.

Each study is reviewed by the SRC to determine if the data and safety monitoring plan is complete and appropriate. In the event that no monitoring is specified by external agencies, the study PI is required to develop a local data and safety monitoring plan that adheres to the following plans:

All investigator-initiated, institutional Phase III clinical trials require regular monitoring by a study-specific, independent DSMB. All such Phase III studies are reviewed by their specific DSMBs periodically, so they are not additionally monitored by the DSMC. However, study progress is reviewed on an annual basis by the DSMC.

The following policies describe DSMC requirements for local, investigator-initiated Phase III trials. They do not replace existing regulations for protection of human subjects, policies and guidelines for conduct of clinical research, inclusion of women and minorities, research project administration, reporting, financial management, or requirements of local Institutional Review Boards (IRBs). DHHS regulations for the protection of human subjects are described in 45 CFR46. The implementation of these regulations for PHS research grants involving human subjects is found in the PHS 398 form (rev. 4/98), available at (http://www.nih.gov/grants/forms.htm).

This policy document describes further steps to be taken to ensure the protection of human subjects when the study involves a potentially harmful intervention, and for other Phase III studies to ensure that participants receive an appropriate share of the benefits.

Protocols for any intervention study should clearly state whether the proposed study meets NIH's criteria for a NIH-defined Phase III trial and the basis for that opinion. The SRC reviews this information. If the protocol does not include the required information for such studies (described below), the protocol is not approved until

this information is received, reviewed, and approved by the SRC.

Therapeutic protocols describe whether the proposed study intervention has potential harmful effects. As part of the review and approval process, the SRC and Stanford University Institutional Review Board (IRB) review the risks of the intervention. If the proposal does not include the required information for such studies (described below), the protocol is not activated until this information is received, reviewed, and approved.

Investigator-initiated Phase III protocols must include:

- Plans for monitoring by either an existing DSMB, or a Stanford DSMC-initiated study specific, independent DSMB, if applicable
- An adequate biostatistical design
- Procedures for quality assurance/quality control, data management, and analysis
- Plans for notifying subjects of trial results after the conclusion of the trial and providing the subjects' health providers with the appropriate information from the trial, as needed, concerning the individual subject (e.g., cessation of drugs, changes in dosage, etc.)

Local reporting for data and safety monitoring for these trials requires all reportable serious adverse events to be reported to the CCTO, DSMC, IRB, and the GCRC or FDA (if applicable).

PHASE II STUDIES

Phase II studies are generally small, with relatively limited numbers of subjects to determine the efficacy of an agent, regimen, device, or procedure and may include correlative biologic or pharmacologic studies. While more is known concerning the risks and benefits of the study treatment as compared with Phase I studies, more subjects are typically exposed to the study regimen. Toxicity and outcomes can be difficult to ascertain due to progression of disease.

A. NIH/NCI-Sponsored Trials

National Cooperative Oncology Group Protocols

Upon initial review of a Phase II cooperative group clinical trial, the Scientific Review Committee verifies that a DSMB, or other structured monitoring plan exists that is overseen by the cooperative group. No further action regarding monitoring takes place on an institutional level, aside from the annual review and serious adverse event reporting.

These trials are multi-institutional and use specific data management systems that allow safety and efficacy data to be closely monitored for each study by site and for the group as a whole. The Cancer Center relies on mandated reporting mechanisms to monitor subjects on these studies, and does not require additional reporting requirements for these trials. However, all SAEs from these trials are required to be reported to the DSMC and IRB. Study progress is reviewed on an annual basis by the DSMC.

Other NIH Grants

In the event that an NCI or other NIH grant supports a Phase II efficacy trial, data and safety monitoring are performed in a manner identical to that for local, investigator-initiated Phase II trials (see section D).

B. Industry-Sponsored Trials

All clinical trials initiated by pharmaceutical industry sponsors with the Stanford University Cancer Center as a participating site require that a data and safety monitoring plan exists. This is verified when the protocol is reviewed by both the SRC and IRB. These protocol-specific plans must adhere to industry and FDA-specified guidelines. The SRC verifies that a monitoring plan exists and is overseen by the study sponsor. No further action regarding monitoring takes place on an institutional level, aside from serious adverse event reporting and an annual review of the study. Local reporting for data and safety monitoring for industry-sponsored trials

requires SAEs to be reported to the CCTO, DSMC, and IRB. Study progress is reviewed on an annual basis by the DSMC.

C. External Peer-Review Trials

Monitoring for these Phase II studies is identical to local, investigator-initiated trials (see section D below). For non-cooperative group, limited-institution Phase II studies without NCI/NIH monitoring, the PI at the lead institution is responsible for the monitoring plan for the study. Prior to activating the study at the Stanford Cancer Center, upon initial review of the protocol, the SRC verifies that a data and safety monitoring plan exists.

Local reporting for data and safety monitoring for these trials requires all SAEs to be reported to the CCTO, DSMC, IRB, OBA, or FDA (if applicable).

As noted previously, investigators must be aware of NIH policy *Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials* (NIH Guide for Grants and Contracts, June 11, 1999), *NIH Policy on Data and Safety Monitoring* (NIH Guide for Grants and Contracts, June 10, 1998), and *Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials* (NIH Guide for Grants and Contracts, June 5, 2000). All these documents are relevant to multicenter, limited-institution trials.

D. Investigator-Initiated Institutional Studies

Once an investigator-initiated, institutional Phase II study has been approved by the SRC, it is the responsibility of the DSMC to monitor serious adverse events and efficacy and to take action as necessary to protect participating subjects from unnecessary risks. Upon initial review of the protocol, the DSMC determines whether a study requires their involvement.

While some variation may exist in monitoring, the DSMC always requires PIs of local, investigator-initiated Phase II studies to provide SAEs to the DSMC for oversight of monitoring. If additional information is required, the DSMC requests that information from the PI. The DSMC tracks findings for the trial as a whole related to cumulative toxicities observed and make recommendations related to continuing, changing, or terminating the trial.

The CCTO Executive Committee and IRB receive and review DSMC reports and recommendations about whether the study should continue unchanged, require modification or an amendment, or be closed based on unacceptable risk to participants. The DSMC then contacts the study's PI. Suspended or terminated trials are reported to the NCI Program Director responsible for the grant supporting the trial, where applicable.

Local reporting for data and safety monitoring for these trials requires on-going SAE reporting to the CCTO, DSMC, IRB, and the OBA or FDA (if applicable). Adverse events which do not meet the definition of an SAE also require timely reporting dependent upon the grade of adverse event using CTC 3.0 criteria and attribution. Safety monitoring uses the same matrix of reporting requirements and schedules as does CTEP, which is available at the CTEP website at http://ctep.info.nih.gov; NCI Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents dated January 2001. All serious adverse event reports must be reported to the CCTO, DSMC, and Stanford University IRB. Study progress is reviewed on an annual basis by the DSMC.

PHASE I STUDIES

These studies are generally small, with limited numbers of subjects to determine a safe and tolerated dose of a drug or regimen and to evaluate adverse events/toxicity. They may also include tumor response evaluation, correlative biologic studies, or pharmacologic studies. Occasionally, Phase I trials evaluate feasibility endpoints in the case of medical devices and procedures. Nevertheless, due to the unknown safety and relatively high risk to the subject from the agent, regimen, or device/procedure under study, these trials require particular attention to monitoring subject safety. The study PI carries the greatest responsibility for subject safety and monitoring in

Phase I trials. Typically, safety parameters are evaluated as follows: with each subject experience and at each treatment level (often including three to six subjects), with an overall assessment of the treatment results (often including thirty or fewer subjects), and at the completion of the study.

A. NIH/NCI Sponsored Trials

National Cooperative Oncology Group Protocols

In the event of a serious and/or unexpected adverse event experienced by a subject on a Phase I cooperative group trial, the NCI requires immediate reporting via the Adverse Event Expedited Reporting System (AdEERS). New guidelines for reporting requirements went into effect on January 1, 2001. Reporting requirements and the timing of reporting are dependent upon the phase of trial, grade of adverse event using CTC 3.0 criteria, attribution, and whether the event is expected or unexpected. A matrix of reporting requirements and schedules is available at the CTEP website at http://ctep.info.nih.gov. All expedited serious adverse event reports must be reported to the IRB and the CCTO. Since extensive monitoring and reporting is required by the NCI/NIH; these Phase I studies do not require additional monitoring or reporting locally.

Other NIH Grants

Other grant mechanisms may provide funding for small pilot, Phase I/II clinical trials of agents for which the NCI/NIH may or may not be the IND holder. Grants supporting these clinical trials are required to provide specific data and safety monitoring plans prior to receipt of funding.

In addition to the usual reporting of all SAEs to the CCTO, DSMC, IRB, and the GCRC or FDA (if applicable), other adverse events are reported to the CCTO using the NCI's AdEERS reporting matrix.

If the study is an investigator-initiated Phase I study, it requires monitoring by the DSMC (see section D). While some variation may exist in monitoring, the DSMC requires PIs to provide SAEs and other reportable AE reports to the DSMC for oversight of monitoring. If additional information is required, the DSMC requests that information from the PI.

B. Industry-Sponsored Trials

All clinical trials initiated by pharmaceutical industry sponsors with Stanford University as a participating site require a data and safety monitoring plan. These protocol-specific plans adhere to industry and FDA-specified guidelines. The SRC verifies that a monitoring plan exists and is overseen by the study sponsor. No further action regarding monitoring takes place on an institutional level, aside from serious adverse event reporting and annual review. Local reporting for data and safety monitoring for industry-sponsored trials requires SAEs to be reported to the CCTO, DSMC, and IRB.

C. External Peer-Review Trials

Monitoring for externally peer-reviewed Phase I studies is identical to local, investigator-initiated trials (see section D below). For non-cooperative group, limited-institution Phase I studies without NCI/NIH monitoring, the PI at the lead institution is responsible for the monitoring plan. Prior to activating the study at the Stanford University Cancer Center, the SRC reviews and approves data and safety monitoring plans.

As noted previously, investigators must be aware of NIH policy *Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-Supported Multicenter Clinical Trials* (NIH Guide for Grants and Contracts, June 11, 1999), *NIH Policy on Data and Safety Monitoring* (NIH Guide for Grants and Contracts, June 10, 1998), and *Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials* (NIH Guide for Grants and Contracts, June 5, 2000). All these documents are relevant to multicenter, limited-institution trials.

D. Investigator-Initiated Institutional Studies

For Phase I studies, the SRC requires the study PI to provide a monitoring plan for subject safety within the study protocol. It is reviewed as part of the full scientific review of the study by the SRC and is also reviewed

by the DSMC.

Once an investigator-initiated, institutional Phase I study has been approved by the SRC and IRB, it is the responsibility of the DSMC to monitor serious adverse events and efficacy and to take action as necessary to protect participants from unnecessary risks. While some variation may exist in monitoring, the DSMC requires PIs of local, investigator-initiated Phase I studies to report SAEs to the DSMC. If additional information is required, the DSMC requests that information from the PI.

Early Phase I trials of agents or regimens with little existing data on toxicity may be of potentially high risk to subjects. If the agent or treatment technique is felt to be of particularly high risk (or is a new method of treatment), the investigator may be required to provide data and safety monitoring reports on a more frequent basis to the DSMC. The frequency of reporting is determined by the DSMC for each specific protocol based on anticipated case enrollment and the specific risks anticipated. The report schedule of individual trials may be modified over the course of the study based on the safety experience of subjects treated.

The DSMC reviews annual data and safety monitoring reports and makes recommendations on whether the study should continue unchanged, requires modification or amendment, or should be closed because of unacceptable risk to participants. The DSMC recommendations are reported to the Protocol Review and Monitoring System Director, CCTO Executive Committee, IRB, and the study PI. Suspended or terminated trials are reported to the NCI Program Director responsible for the grant supporting the trial, where applicable.

In the event of an SAE experienced by a subject on a local, investigator-initiated Phase I trial, the study PI is required to report the SAE to the CCTO, DSMC, IRB, and FDA (if applicable) using appropriate reporting forms.

Appendix IV: Protocol Monitoring Form

Annual Renewal	Stanford University Cancer Center Data and Safety Monitoring Committee

Protocol: _____

P.I.: _____

_____

Designated CRA or research nurse clinician: _____

Statistician: _____ No statistician named: _____

Phase of study: _____

Type: Registration only: _____ Randomized: _____ Both (e.g., multiphase): _____

Site(s): Stanford only: _____ Multicenter _____

IRB#: _____

Monitoring Team or Annual Reviewer: _____

IRB (to be completed by DSMC):

1. Initial IRB approval date:
2. Date of last IRB renewal: _____

Comments: _____

PREVIOUS DSMC REVIEWS (to be completed by DSMC):

1. Review date: _____ Rating: _____ Comment: _____
2. Review date: _____ Rating: _____ Comment: _____
3. Review date: _____ Rating: _____ Comment: _____

ACCRUAL (to be completed by DSMC):

Current accrual: _____ as of: _____ In Oncore O Yes O No

Targeted accrual: _____

Date first subject enrolled: _____

Date most recent subject enrolled: _____

Projected duration of study: _____

Comments: _____

Appendix V: Protocol Registration Form

Protocol Registration Form

Stanford University Cancer Center
Cancer Clinical Trials Office (CCTO)

Submit this form to CCTO including electronic copies of
Protocol, Amendments, Consent Forms and e-Protocol or IRB application
Email: CCTO-Protocol@stanford.edu
Fax: 650-736-2558
Phone: 650-736-0421
http://cancertrials.stanford.edu/ctoffice.html

Required Information for All Studies

IRB Protocol No:	**e-Protocol ID:**	*For CCTO use only – Oncore Protocol #:*
Protocol Title:		
Concise Protocol Title (100 characters max):		
Study Site/Hospital (Select all that apply)	☐ Stanford Cancer Center ☐ GCRC ☐ Lucille Packard Children's Hospital ☐ Peds GCRC ☐ VA Medical Center	
Phase	☐ Phase I ☐ Phase I/II ☐ Phase II ☐ Phase II/III ☐ Phase III ☐ Phase IV ☐ Pilot ☐ N/A ☐ Feasibility	

Treatment Type	☐ Therapeutic ☐ Prevention (Non-Therapeutic) ☐ Non-Treatment (Ancillary/Companion/Correlative)	
Age Limits	Minimum: _____ ☐ Years ☐ Months ☐ N/A (No Limit)	Maximum: _____ ☐ Years ☐ Months ☐ N/A (No Limit)
Gender	☐ Both ☐ Female ☐ Male	
Scope (Check all that apply)	☐ **Stanford Investigator-Initiated Study** ☐ **Stanford Only** ☐ Multi-site ☐ National Cooperative Group Study ☐ **Stanford Lead PI / Study Chair** ☐ Sponsor-Initiated Study	
Accrual Numbers		Protocol Target Accrual – Stanford
		Annual Accrual Goal – Stanford
		If Stanford is the lead for a multi-site study, enter Protocol Target Accrual for entire study across all participating sites
Toxicity Scheme	☐ CTC v2 ☐ CTC v3 ☐ CTC v4	
Study Agents ☐ *Use agents from e-Protocol (#6 & #7)*		

DISEASE SITE / CANCER CATEGORY (Select all that apply)

☐ Cutaneous Lymphoma	☐ Bones and Joints
☐ Melanoma, Skin	☐ Spine
☐ Kaposi's Sarcoma	☐ Head & Neck Cancer
☐ Mycosis Fungoides	☐ Lip, Oral Cavity and Pharynx
☐ Other Skin	☐ Esophagus
☐ Soft Tissue / Sarcoma	☐ Larynx
☐ Stomach	☐ Eye and Orbit
☐ Small Intestine	☐ Brain and Nervous System
☐ Colon	☐ Thyroid
☐ Rectum	☐ Other Endocrine System
☐ Anus	☐ Lung
☐ Liver	☐ Other Respiratory/Intrathoracic Organs
☐ Pancreas	☐ Non-Hodgkin's Lymphoma
☐ Other Digestive Organ	☐ Hodgkin's Lymphoma
☐ Urinary Bladder	☐ Multiple Myeloma
☐ Kidney	☐ Lymphoid Leukemia
☐ Other Urinary	☐ Myeloid and Monocytic Leukemia
☐ Breast - Female	☐ Leukemia, other
☐ Breast - Male	☐ Leukemia, not otherwise specified
☐ Cervix	☐ Other Hematopoietic
☐ Corpus Uteri	☐ Myelodysplastic Syndromes
☐ Endometrial Cancer	☐ Myeloproliferative Disorders
☐ Ovary	☐ Bone Marrow/Stem Cell Transplantation
☐ Other Female Genital	☐ Unknown Sites
☐ Prostate	☐ Ill-Defined Sites
☐ Testicles	☐ Any Site
☐ Other Male Genital	☐ Rare Cancers

Clinical Research Category	☐ Agent/Device ☐ Other Interventions ☐ Epidemiologic/Observational ☐ Companion/Ancillary/Correlative	**CCC PROGRAM** (Select One)	**RESEARCH STAFF** (Add others in Comments)
Primary Sponsor	☐ Stanford University ☐ NIH – Funding Agency: _____ ☐ Industry – Name: _____	☐ Cancer Stem Cell Research ☐ Radiation Biology ☐ Cancer Biology ☐ Cancer Imaging ☐ Molecular Profiling ☐ Lymphoma Hodgkin's ☐ Immunology & Immunotherapy ☐ HCT & Immune Reconstitution ☐ Cancer Epidemiology ☐ Cancer Prevention ☐ Solid Tumors ☐ Experimental Therapeutics	Lead PI Co-Investigator Co-Investigator Co-Investigator Fellow RN Study Coordinator CRA Data Manager
Sponsor Protocol #			
Other Sponsors			
IRB APPROVAL, PROTOCOL OPEN & CLOSE DATES			
Date Submitted to IRB & SRC		Includes Follow-up? ☐ Yes ☐ No	**Primary Study Contact** (Website & Pocket Guide)

IRB Protocol No:	e-Protocol ID:	For CCTO use only – Oncore Protocol #:		
Protocol Title:				
IRB Initial Review Approval Date		Other protocol actions:	Name	
Date Protocol Opened to Accrual		☐ Suspended Date: ____	Email	
Date Protocol Closed to Accrual		☐ Terminated Date: ____	Phone	
Final Protocol Closure Date	Reason		*Comments:*	

Form Completed by ____ *Date* ____ *Phone* ____

Additional Information for Posting Study on Stanford Clinical Trials and ClinicalTrials.Gov websites

IRB Protocol No:	e-Protocol ID:	Oncore Protocol #:

☐ Post study on **Stanford Clinical Trials** website (only **Trial Type** is required – all other information is optional)

☐ Post study on **ClinicalTrials.Gov** website (**ALL** information is required)

Trial Type: ☐ Diagnostic ☐ Genetics ☐ Prevention ☐ Screening ☐ Supportive ☐ Treatment ☐ Unspecified

Additional information required for posting on ClinicalTrials.Gov and optional for posting on Stanford Clinical Trials website

☐ IND ☐ IDE ☐ N/A	IND/IDE #:	Serial #:	Grantor: ☐ CDER ☐ CBER ☐ CDRH

STUDY OBJECTIVES AND DESIGN (include introductory paragraph, conditions treated, and treatments or interventions)

Brief Summary:

Detailed Description: ☐ *use description from Protocol or e-Protocol*

Intervention Name (List all that apply)	**Intervention Type** (Select one type per intervention) ☐ *use Study Agents for Drug interventions*
	☐ Drug ☐ Device ☐ Procedure ☐ Behavior ☐ Vaccine ☐ Gene Transfer
	☐ Drug ☐ Device ☐ Procedure ☐ Behavior ☐ Vaccine ☐ Gene Transfer
	☐ Drug ☐ Device ☐ Procedure ☐ Behavior ☐ Vaccine ☐ Gene Transfer

OUTCOMES (specific measures or observations used to measure the effect of experimental variables) ☐ *use info from Protocol or e-Protocol*

Primary Outcomes:

Secondary Outcomes:

KEY ELIGIBILITY (INCLUSION/EXCLUSION) CRITERIA: ☐ *use criteria from Protocol or e-Protocol*

CONDITIONS & KEYWORDS	☐ **INTERVENTIONAL STUDY**		☐ **OBSERVATIONAL STUDY**
Use the National Library of Medicine's Medical Subject Headings (MeSH) at http://www.nlm.nih.gov/mesh/MBrowser.html **Conditions:** *Primary diseases or conditions being studied. Enter up to 5 disease or condition terms.* **Keywords:**	**Purpose** ☐ Treatment ☐ Prevention ☐ Diagnosis ☐ Educational/Counseling/Training **Allocation** ☐ Randomized Controlled Trial ☐ Nonrandomized Trial **Endpoint** – (OPTIONAL) ☐ Safety ☐ Efficacy ☐ Safety/Efficacy ☐ Bio-equivalence ☐ Bio-availability ☐ Pharmacokinetics ☐ Pharmacodynamics ☐ Pharmacokinetics/dynamics	**Masking** ☐ Open ☐ Single Blind ☐ Double Blind **Control** ☐ Placebo ☐ Active ☐ Uncontrolled ☐ Historical ☐ Dose Comparison **Assignment** ☐ Single Group ☐ Parallel ☐ Cross-over ☐ Factorial ☐ Expanded Access	**Purpose** ☐ Natural History ☐ Screening ☐ Psychosocial **Duration** ☐ Longitudinal ☐ Cross-sectional **Selection** ☐ Convenience Sample ☐ Defined Population ☐ Random Sample ☐ Case Control **Timing** ☐ Retrospective ☐ Prospective ☐ Both

Appendix VI: Subject Registration Form

Subject Registration and On/Off Study Form
Stanford University Cancer Center
Cancer Clinical Trials Office (CCTO)

Enter REQUIRED data into Oncore, or
Submit to CCTO *via ID Mail MC 5548; mark as* CONFIDENTIAL
Oncore Support: 650-736-0421
http://cancertrials.stanford.edu/ctoffice.html

Study Site (Hospital): ☐ Stanford Cancer Center ☐ Lucille Packard Children's Hospital ☐ VA Medical Center		
IRB Protocol No.:	☐ Protocol application submitted via e-Protocol **e-Protocol ID:**	*For CCTO Use Only* Oncore Protocol No:

SUBJECT DEMOGRAPHICS (REQUIRED)

Medical Record No.		Ethnicity	☐ Hispanic or Latino ☐ Non-Hispanic ☐ Unknown
Last Name			
First Name			
Date of Birth	Approx.? ☐ Yes ☐ No	Race (Check all that apply)	☐ American Indian/Alaskan Native ☐ Asian ☐ Black/African American ☐ Native Hawaiian/Pacific Islander ☐ White ☐ Unknown ☐ Subject Refusal
Gender	☐ Male ☐ Female ☐ Other		

SUBJECT ON STUDY INFORMATION (REQUIRED)

Sequence No.	
On Study Date	

DISEASE SITE (REQUIRED)

Disease Site	ICD-O-3 Code*:
	Description*:

HISTOLOGY (REQUIRED)

Histology	ICD-O-3 Code*:
	Description*:

** Select from CCTO Disease Site and Histology ICD-O-3 Lists*

SUBJECT HOME LOCATION (OPTIONAL)

City	
State	
Zip Code	

CONSENT FORMS (OPTIONAL)

Consent Form Version Date	
Research Consent & HIPAA Consent Signed Date	

TREATMENT STAFF (OPTIONAL)

Treating MD	
Treating RN	
Treating CRA	
Treating Fellow	

SUBJECT TREATMENT INFORMATION (OPTIONAL)

Arm Assignment Code and Description:	
Treatment Dose Level, If Applicable:	
Arm Assignment Date	
On Treatment Date	

SUBJECT OFF-STUDY OR FOLLOW-UP INFORMATION

Follow-up Site (Hospital)		Off Study Reason	☐ Assigned treatment completed ☐ Death w/o progressive disease ☐ Error (taken off study in error) ☐ Excessive complication/toxicity ☐ Maximum dose reached ☐ Other ☐ Other complicating disease ☐ Pt. started non-protocol therapy ☐ Pt. withdrawal or refusal ☐ Progressive disease
Alternate MRN			
Off Treatment Date			
Off Study Date			
Expired Date	Approx.? ☐ Yes ☐ No		

Form Completed by _____

Date _____

Appendix VII: Timeline for Conducting a Monitoring Session

Steps Prior to Monitoring Session	Preparations by PRMS Coordinator
Determine Trial and Subjects	1. Generate list of trials to be monitored. 2. Generate random subject records to be monitored for each trial.
Notification	1. Notify PI and support staff of study selection and monitoring date, subject list, and materials to prepare for the monitoring session. 2. Identify the Monitoring Team members for each protocol. 3. Reserve room for monitoring session.
Material Preparation	1. Request medical records. 2. Request other materials if necessary. 3. Get copies of the protocols and related documentation. 4. Get copies of SAEs/Notes to file/other subject-related correspondence for the monitoring session. 5. Finalize Monitoring Teams and inform members of meeting arrangements.
Meeting Preparation	1. Email copies of protocol to Monitoring Team members for review. 2. Make two paper copies of the protocol and flag them by section for quick reference. 3. Ensure receipt of lab logs, if needed. 4. Regulatory documentation is reviewed by the CRA/Monitor Coordinator. 5. Sort and group the following – medical records, shadow charts, CRFs. 6. Lab logs and regulatory paperwork – may be centralized in one file. 7. Make sufficient copies of monitoring forms; insert date and protocol-specific events. 8. Collect sufficient numbers of BSA calculators, CTC guides, copies of 3-year calendar, pencils, notepads, post its, etc.

Appendix VIII: Monitoring Question List - Regulatory

Stanford University Cancer Center

Monitoring Question List - Regulatory
Treatment Studies

Study:	
Reviewer:	
Date	

IRB Approvals

Consent Forms	**Yes**	**No**	**N/A**
Is the consent form current?			
Is HIPPA authorization current?			

Comments:

Initial Approval	**Yes**	**No**
Is there a copy of the original IRB submission and approval?		
Is there an SRC approval letter?		

Comments:

Amendments	**Yes**	**No**	**N/A**
Are there IRB approvals for each amendment?			

Comments:

Renewals	**Yes**	**No**
DSMC - Are there DSMC approvals for each renewal while the study is open to enrollment?		
Are there IRB approvals for each renewal and were they approved prior to the expiration date? If not, record exp. date and date approved in the Comments section.		

Comments:

Miscellaneous	**Yes**	**No**	**N/A**
Is there an investigator brochure and was it submitted to the IRB?			
Are copies of DSMC submissions and letters present?			
Are GCRC approvals present if applicable?			
Is radiation safety* approval present if required?			

* Only required for situations when subjects are receiving radiation outside of standard of care, for example radio-labeled investigational drugs are being used or radiation therapy doses outside the standard ranges.

For Investigator-Initiated Studies Only

IND	Yes	No	N/A
Who holds the IND? _____ *If not held by a drug company, answer the following questions:*			
Is the original IND submission present?			
Were the protocol amendments submitted to the FDA?			
Are copies of IND annual reports present?			
Was an IND exemption obtained?			
Is this a CTEP study? _____ If so, did they take care of IND documentation? _____			

Comments:

Regulatory Documents	Yes	No	N/A
1572 (for IND studies only)			
Signed PI signature page for each amendment			
CVs for all investigators?			
Medical licenses for all investigators			
CLIAs and CAPs (if applicable)			
Normal Ranges?			
IRB Rosters?			
Financial Disclosures?			

Comments:

For Investigator-Initiated Multicenter Studies

IRB Approvals	Yes	No
Is there a current approved consent form and HIPAA authorization for every site?		
Is there an IRB approval for the original submission and any amendments?		
Are there IRB approvals for each renewal and were they approved prior to the expiration date? If not, record exp. date and the date approved in Comments		
SAE Submissions: Have all SAEs been submitted to the IRB? # of SAEs Reported**:** ____ # of SAEs Acknowledged: _____		
Have all SAEs been reported to **FDA** and/or **NCI**?		

Comments:

Regulatory Documents for Each Site	Yes	No	N/A
Medical licenses for all investigators for each year they have been listed on the study?			
CVs for all investigators (updated at least every 2 years)?			
CLIAs and CAPs (if applicable)?			
Normal Ranges? Quest Labs			
IRB Rosters?			
1572 (for IND studies only)?			

Comments:

Appendix IX: Stanford DSMC Reporting Requirements for Serious Adverse Events

Protocol Directors/Principal Investigators (PDs/PIs) are responsible for reporting any serious adverse events (SAEs) to both the IRB and regulatory authorities. Stanford's Human Subject Manual defines reportable events as "all serious adverse events, related or unrelated to the study treatment, occurring at Stanford or elsewhere, and unanticipated problems." The panel has established the reporting timeline as within five to fifteen days of first learning of the event. PDs and PIs must also report any SAEs to the biopharmaceutical sponsor or FDA (when the PD acts as sponsor-investigator) according to 21 CFR 312.32. By definition, a serious adverse event is any untoward or unexpected event or medical occurrence, associated with the use of a drug that at any dose: results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. The term "unexpected" refers to the specificity or severity of the event and is used to further quantify an event/experience when it is not consistent with the current investigator brochure or with the risk information in the investigational plan. "Associated" with the investigational drug/biologic/device means that there is a reasonable possibility that the experience/event may have been caused by the drug or was contributed to, at least in part, by the drug. Finally, a "life -threatening" event means that in the view of the investigator, the event places the subject or subject at immediate risk of death from the reaction as it occurred. Timelines for reporting SAEs to sponsors or the FDA are more specific and depend on the outcome of the event (hospitalization, disability, death).

PDs and PIs are responsible for adhering to the timelines for reporting SAEs. When the Protocol Director is the Principal Investigator for an NIH/NCI sponsored study, the investigator must notify the Investigational Drug Branch (IDB) of the NCI by telephone of all Grade 4 and Grade 5 expected and unexpected events (see the Common Toxicity Criteria Index @ www.ctep.nih.gov) within 24 hours of learning of the event. In addition, all Grade 4 and Grade 5 expected and unexpected events, all unexpected Grade 2 and 3 events, and all late deaths, regardless of attribution, must be reported via the AdEERS system within ten days of learning of the event.

When a biopharmaceutical company sponsors a study, the Principal Investigator reports all SAEs that meet the definition given in the specified protocol to the Sponsor. Any unexpected death or life-threatening event experienced by a subject on a clinical trial that utilizes an investigational agent, requires prompt notification of the FDA by the sponsor's drug safety group. Often sponsors request notification via telephone within 24 hours of any event regardless of severity. In addition, specific protocol-specific adverse event case report forms must be completed and continued close follow up is required until the event resolves.

When a Protocol Director is both the Principal Investigator and sponsor of a clinical trial (investigator-initiated), the requirements for reporting all SAEs to the FDA and other investigator rest with the PD. Specifically, the PD must notify the FDA of any study-related death or life-threatening event via telephone within 24 hours of learning of the event. A written safety report (Medwatch 3500A) must be sent to the FDA within seven days. Any other investigators who are participating in the study must be notified via an IND Safety Report within 15 days of learning of the event.