

# Data and Safety Monitoring Plan (DSMP)



**UCSF** Helen Diller Family  
Comprehensive  
Cancer Center

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# **Data and Safety Monitoring Plan**

## **UCSF Helen Diller Family Comprehensive Cancer Center**

### **I. Introduction**

#### **UCSF Helen Diller Family Comprehensive Cancer Center Overview**

The University of California at San Francisco Helen Diller Family Comprehensive Cancer Center (HDFCCC) is a National Cancer Institute (NCI) designated matrix center conducting a wide range of interdisciplinary research in the areas of laboratory, clinical, and population sciences. The HDFCCC is led by the Director of the Center, who is assisted by the Deputy Director. The remainder of senior leadership is comprised of Associate Directors of: Laboratory Research, Clinical Research, Population Science Research, Shared Resources, Education and Training and Administration.

#### **Operational Definition of a Clinical Trial (NCI definition)**

For purposes of the Data and Safety Monitoring Plan (DSMP), a clinical trial is operationally defined as a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions. Clinical trials may be described as therapeutic or non-therapeutic interventions and can include drugs, treatments, devices, as well as behavioral or nutritional strategies. Participants in these trials are patients with a diagnosis of cancer, or, in the case of primary prevention studies, at risk for cancer. Behavioral clinical trials include 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 effect of treatment. These non-therapeutic interventional trials may pertain to cancer prevention, screening and early detection, symptom management, and survivorship.

In the area of molecular or imaging diagnostics, a study is a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subjects. In this way, a key goal of the trial is to collect diagnostic information that has an impact on some aspect of outcomes or clinical assessments. By contrast, studies which 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 minimal risk trials and are not covered by this DSMP. The exception to this would be if performing the diagnostic test itself imposes some risk on study subjects.

Observational and epidemiological studies and those that do not test interventions are minimal risk trials and, thus, are not covered by this DSMP.

## **II. Responsibilities of the Component Units of the Helen Diller Family Comprehensive Cancer Center Clinical Trials Operations**

- **The Cancer Center Clinical Trials Oversight Committee (CCCROC)**

The **CCCROC** provides oversight to the Clinical Protocol and Data Management (CPDM) and the Protocol Review and Monitoring System (PRMS) (see Appendix A). The CPDM includes the Clinical Research Support Office (CRSO), and the Data and Safety Monitoring Committee (DSMC). The CRSO, PRMS, and the DSMC are independent units whose activity is overseen and integrated by the CCCROC. The CRSO, PRMS, and the DSMC are each led by an experienced senior faculty member and a seasoned operations staff manager. The faculty members of these units are responsible to the CCCROC, which is chaired by the Deputy Director and the staff managers of each of these units report to the Associate Director of Administration. The Deputy Director reports to the HDFCCC President and Director.

- **Protocol Review and Monitoring System (PRMS)**

The **PRMS**'s goal is to promote optimal review of the scientific merit, priorities and progress of all clinical research at the HDFCCC. PRMS functions are accomplished by rigorous review in a two-stage review process consisting of (1) disease-focused Site Committees and modality Site Committees, where initial scientific review, assessment of clinical protocol feasibility and projected accrual rates, and prioritization is undertaken; and (2) the Protocol Review Committee (PRC). The scope of the PRC review encompasses the scientific rationale, study design, expected accrual rates, adequacy of biostatistical input, feasibility of trial completion within an appropriate time period, prioritization in terms of scientific merit and patient availability, and ongoing review of scientific progress including reasonable study goals and accrual rates. The PRC is also charged with overall prioritization of all trials across the center. As described below, Site Committee review and approval is required before PRC review of a trial. Although input and review from Site Committees is a critical component of the PRMS process, the PRC has final PRMS authority regarding review, approval, monitoring and closure of trials. The PRC meets monthly.

- **Site Committees**

Each element of the clinical trials infrastructure (CRSO, DSMC, and PRMS) interfaces with clinical investigators through the **Site Committees**. HDFCCC clinical investigators are required to participate in a disease- or modality-specific Site Committee. There are 14 Site Committees; ten are disease specific and four are modality specific (Appendix D). All CCSG Programs with a major clinical component have designated Site Committees.

In addition to protocol review, prioritization, and accrual and scientific relevance monitoring, Site Committees are responsible for the development, activation, and conduct of clinical trials. The DSMC conducts its audit functions by interfacing with Site Committees, and Site Committees monitor toxicities associated with its trials.

This is achieved through the CRSO, as described below. Site Committees meet at least monthly, and committees reviewing phase I or high risk trials are required to meet weekly.

- **Clinical Research Support Office (CRSO)**

The **CRSO** is composed of a Regulatory Affairs Unit and a Research Personnel Unit (Appendix B). The Regulatory Affairs Unit is responsible for protocol development of institutional trials, patient safety monitoring and reporting, federal compliance, protection of human subjects, and regulatory training for study team staff. The Research Personnel Unit is responsible for recruitment, hiring, onboarding, training, supervision, and performance management of all clinical research coordinators (CRCs). CRCs are responsible for the daily operations and execution of study protocols after activation, including source document collection, data entry, patient visit coordination and navigation, and monitoring visits. The Protocol Review and Monitoring System provides the scientific review and protocol feasibility, while the Data and Safety Monitoring Committee provides the monitoring and auditing oversight, for the trials conducted by the CRSO.

- **UCSF Institutional Review Board (IRB)**

The **IRB** is comprised of four committees (Laurel Heights Committee, Mt. Zion Committee, Parnassus Committee, and the Zuckerberg San Francisco General Hospital Committee) that share equal authority and responsibility. Each of the four panels meets twice a month, so that overall eight IRB meetings are held each month. Following PRC approval, the IRB reviews all HDFCCC protocols and determines final status (approval/disapproval) of each protocol.

- **The Data and Safety Monitoring Committee (DSMC)**

The **DSMC** is responsible for monitoring and auditing institutional trials for data validity, trial conduct, and serious adverse event (SAE) reporting. The risk assessment of the trial is determined by the phase of the trial, which in turn, designates the frequency of monitoring (see Appendix H). The HDFCCC Director appoints the faculty director of the DSMC. The DSMC Director together with the Deputy Director appoints other members of the DSMC. There DSMC members may serve in the committee indefinitely, as there is not a term limit. The DSMC meets every six weeks.

- Activities of the DSMC are overseen by CCCROC (Appendix A). The DSMC Director provides reports to the HDFCCC Director, Deputy Director, and

CCCROC detailing DSM activities. Additionally, the minutes of each DSMC meeting are provided for review by the Deputy Director. When the DSMC identifies areas of concern, in addition to conferring with the Deputy Director, the DSMC Director notifies the Protocol Review Committee (PRC), CCCROC, and the UCSF IRB as warranted. The DSMC manager oversees the DSM Monitors and the Education and Training Coordinator (Appendix C).

- *Phase I Institutional Trials*

These trials are monitored (i.e., reviewed in real time) monthly, beginning one month after the enrollment of the first patient. In addition, all patients in each cohort are monitored prior to the approval to dose escalation. The DSMC chair reviews the DSMC monitoring report or obtains a verbal report from the DSMC monitor. Dose escalations are approved by the DSMC Chair or qualified alternate (i.e., Vice Chair) within two business days of the request. The DSMC monitoring report is then reviewed at the subsequent DSMC meeting. In the event that the committee does not concur with the DSMC Chair's decision, accrual is held while further investigation takes place.

- *Phase II and III Institutional Trials*

These trials are audited (i.e., reviewed retrospectively) twice per year, with all data from twenty percent of the enrolled patients reviewed by the DSMC Monitor.

- The regulatory files for all Institutional Trials are audited annually by the DSMC for regulatory compliance.
- DSMC monitoring reports are reviewed at the DSMC meeting following the monitoring visit(s). The DSMC may request additional data or add recommendations. After the DSMC Chair approves the monitoring report, the report is then sent via e-mail to the PI and study team for follow-up. If serious non-compliance is identified during the monitoring visit, the DSMC will recommend to the DSMC Chair that a voluntary suspension on accrual be implemented while the PI and study team develop a corrective and preventative action (CAPA) plan. If there are serious or continuing compliance issues or an increased risk to subject safety in a study trial or study program, the DSMC may mandate a temporary enrollment suspension for a trial or a study program until a robust Corrective and Preventative Action (CAPA) plan is developed by the PI and study team. The DSMC Manager will notify the Industry Sponsor (i.e., Pharmaceutical Sponsor) and the NCI Program Director for NCI-CTEP trials of this suspension on trial activities. Once the suspension has been lifted by the DSMC, then the DSMC Manager will then notify the Industry Sponsor for

Industry-Sponsored trials and the NCI Program Director for NCI-CTEP trials of the lifting of this suspension on trial activities.

### **III. Data and Safety Monitoring Plan: Required Elements**

All clinical trials conducted at the UCSF HDFCCC, except for minimal risk trials, must have a satisfactory DSMP, which is described in detail in the protocol. These plans will be reviewed by the PRC as part of the protocol approval process and are evaluated in relation to the potential risks and scale of the trial (see appendix H).

Elements of a Data and Safety Monitoring Plan (DSMP) include:

#### **A. Delineation of responsibilities:**

For all therapeutic and non-therapeutic interventional trials, the Principal Investigator (PI) is responsible for the supervision of the protocol conduct, patient consent procedure, patient enrollment, and collection of data, adverse event reporting, and ensuring that the protocol has current IRB approval. The Principal Investigator is also responsible for reporting of safety-related events to the HDFCCC DSMC, the UCSF IRB, the participating sites for multicenter studies (when UCSF is the Coordinating site), federal regulators (i.e., FDA) when the trial is conducted under an Investigational New Drug Application (IND, and the NCI CTEP (as applicable).

### **IV. Guidelines for Data and Safety Monitoring Implementation**

A. Principal Investigators will conduct review of data and patient safety at Site Committee meetings. Phase I trials will undergo weekly review and Phase II and III trials will undergo monthly review. Discussion and conclusions will be documented in the Site Committee meeting minutes. The discussion should include the following elements:

- Screening, new patient enrollment, and accrual rates.
- A per patient review of:
  - Significant toxicities as described in the protocol.
  - Grading of all significant toxicities.
  - Attribution of the relationship of the toxicity to the study drug.
  - Determination whether a toxicity was expected or unexpected.
  - Dose modifications per protocol.
  - Efficacy.
  - Rate of occurrence of adverse events as compared to the investigators brochure or package insert.



- B. Phase I-III therapeutic interventional clinical trials above minimal risk must have a DSMP that is directed toward the anticipated risks of the study and is commensurate with the level of risk to the participants. The DSMP must be included in the research proposal and must be approved by the PRC prior to opening the study.

## **V. Implementation of Reporting Requirements**

### **A. Serious Adverse Event (SAE) Reporting**

- The DSMC reviews all SAE Reports for all clinical trials (i.e., Industry-Sponsored, Institutional, and Cooperative Group) via an OnCore Report at the DSMC Meetings, which occur every 6 weeks.
- All deaths related to the Investigational Product or Investigational Device must be reported by the Principal Investigator (PI) to the DSMC chair within one business day.
- All SAEs, regardless of the relationship to the study, will be tracked in OnCore®, the UCSF HDFCCC data management tool.
- The Principal Investigator (or Study Chair) shall be responsible for notification of other participating institutions if the clinical trial involves multiple institutions and UCSF is the lead institution according to the protocol.

### **B. Study Progress**

- The DSMC will use DSMC monitoring reports and protocol stopping rules to determine whether a study warrants closure.
- All external audits must be submitted to the DSMC, whether from Industry Sponsor audits or from NCI audits for review at DSMC meetings.
- The recommendations of the DSMC are forwarded to the Deputy Director of the HDFCCC. The Deputy Director of the HDFCCC and the DSMC Chair will provide communication to the IRB of any decisions for enrollment suspension within a study program for study non-compliance issues.

## **VI. Monitoring Procedure**

The PRC determines the level of risk, which in turn, determines the monitoring/auditing frequency as outlined in Appendix H. The DSMC Monitor manages the logistics associated with the monitoring review sessions. Once the clinical trial is identified for monitoring, the DSMC Monitor arranges for a selection of cases to monitor from among the subjects registered in OnCore® based upon the guidelines in Appendix H. The Principal Investigator and Study Coordinators are notified via e-mail in advance of a scheduled monitoring session

to arrange a mutually agreed upon time for the monitoring session. The investigator and research staff are responsible for gathering all of the materials needed for this review, including medical charts and other research records requested. For Multicenter trials, the participating sites are responsible for downloading the redacted source documents in the PC console of OnCore® for the DSMC Monitor to monitor/audit.

The DSMC Monitor reviews the regulatory files once per year when the trial is audited. The DSMC Monitor uses OnCore® and iRIS® to review the following in the trials reviewed:

- approval dates for protocols and amendments with no lapses in ongoing approvals.
- approved informed consent forms (ICF).
- approved study documents (e.g., patient diaries).
- SAEs and PV Reports to the IRB.
- Approved Protocol Eligibility Exceptions (PEE).
- IND Safety Reports.

Additionally, the DSMC reviews the following:

- The DSMC Monitor reviews the medical records as the source documents and verifies data entry in the electronic case report forms (OnCore®). The source documents are reviewed to ensure that there is adherence to the protocol and to identify if there are safety issues with the conduct of the study.
- Informed consent forms, HIPAA, and Bill of Rights documents properly obtained.
- Any required pre-study tests and procedures are obtained within the designated pre-treatment time interval.
- All eligibility criteria reviewed to ensure that the study patient is qualified for the trial.
- Adherence to treatment plan is documented, including Investigational Product (IP) orders, drug doses and dose reductions and/or treatment holds, if indicated.
- Accuracy, adequacy, completeness, and timeliness of data collection and submission.
- Appropriate and timely recording of adverse events (AEs) and reporting serious adverse events (SAEs) to the UCSF IRB.
- Review of possible dose limiting toxicities (DLTs).
- Adherence to patient follow-up requirements.

Following the completion of the monitoring session, the DSMC Monitor will complete the Monitoring Report (see Appendix G), which describes the findings of this monitoring

visit. The study is given an overall evaluation by the DSMC Monitor (and approved by the DSMC Chair) of one of the following evaluations:

- Satisfactory (no follow-up required).
- Acceptable with follow-up items to be completed.
- Significant findings, with follow-up response to DSMC required.
- Unsatisfactory, halt enrollment of new subjects, corrective action plan required within 10 days to the DSMC. The DSMC Chair will notify the IRB regarding the results of this audit/monitoring visit

This evaluation is based upon the findings of the monitoring visit(s) and includes GCP compliance issues, subject safety issues, and protocol adherence issues. In rating the conduct of the study, the DSMC categorizes variances from the protocol as protocol violations. Major Protocol Violations are variances from the clinical trial-specified criteria or procedures that make the resulting data questionable and can affect patient safety. Examples of these would include failure to obtain informed consent prior to study related procedures or treatment or not reporting dose limiting toxicities. Minor Protocol Violations (or Protocol Deviations) are variances that do not affect the outcome or interpretation of the study or the safety of the study participants. Examples of these would include the investigator not grading the clinical significance of an abnormal lab or ECG or a patient occasionally forgetting to take the study drug during the study.

The significant findings of the DSMC Report are presented to the DSMC Chair and the DSMC Committee. The DSMC Committee votes on the following recommendations:

- **Full Approval:** Enrollment may continue; no outstanding questions regarding toxicity and/or accrual.
- **Conditional Approval:** Enrollment may continue conditionally 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 violations.
- **Closure:** Study is closed due to unacceptable study conduct and toxicities.

The DSMC Committee's decision is sent to the trial's Principal Investigator in writing, along with a copy of the monitoring report. If the Principal Investigator decides to appeal the DSMC decision, he/she may do so in writing. If the appeal is unsatisfactory, the Principal Investigator may appeal to the Deputy Director.

## **VII. Data Quality Control**

### **A. Pre-Industry Sponsored Audit and Pre-FDA Inspection DSMC Review**

The DSMC will conduct a trial review prior to an Industry-Sponsored Quality Assurance audit, which is completed in preparation for a potential FDA Inspection. Additionally, the DSMC will conduct a pre-FDA Inspection Review in order to prepare the trial for a scheduled FDA Inspection. Both reviews will include a review of compliance for regulatory adherence, study patient review, and pharmacy review. For each DSMC review, the DSMC Monitor will review at a minimum:

- Informed consent.
- Eligibility.
- Randomization documentation (if applicable).
- Adherence to the protocol: protocol deviations/violations.
- Administration of drug, study drug orders, and dose adjustments due to adverse events per protocol.
- Recording of adverse events including CTCAE version 4.03 grading and attribution of each event
- Reporting of serious adverse events (SAEs)
- Evaluation of disease progression and tumor measurement (RECIST)
- Review of Regulatory files.
- Review of Pharmacy records.

The findings from these DSMC Reviews will be discussed with the PI and the study team and all issues will be resolved prior to either the Sponsor QA visit or the FDA Inspection. This may include the submission of reportable Protocol Violations with a Corrective and Preventative Action Plan (CAPA).

### **A. Education and Training for Study Staff**

The Education and Training Coordinator (ETC) is a member of the DSMC and reports to the DSMC Manager. The ETC is responsible for the development of the onboarding and refresher-training curriculums for CRCs, PPMs, and the PIs (see Appendix F).

In addition to the UCSF required onboarding, including Collaborative Institutional Training Initiative (CITI) Good Clinical Practice (GCP) and Human Subjects Protection, and Health Insurance Portability and Accountability Act (HIPAA) training, the CRC onboarding series is offered every six weeks and is required for all new Cancer Center

CRCs to attend. The training is led by Senior and Lead CRCs and organized by the Education and Training Coordinator.

All HDFCCC investigators are required to complete a comprehensive PI training program on the proper conduct of clinical research. New investigators are required to complete their training before being added as Investigator (i.e., listed on the FDA 1572 form) on any study in the HDFCCC. Investigators will be required to re-train every three years. The investigator-training program was implemented in October 2016. The PI training is conducted by the Education and Training Coordinator and the Manager of the Data Safety and Monitoring Committee.

## **B. Remediation Process**

If there are significant safety issues within a study program (i.e., numerous Serious Noncompliance Determinations from the IRB or a significant loss of study staff) which put study patients at risk and affect the integrity of the data in the clinical trial(s), then the DSMC may place the study program on a mandatory enrollment suspension until these issues are resolved (Appendix I). The DSMC Manager and the DSMC Chair will communicate this decision to the Deputy Director and CCCROC, as well as notify the PI and the study team of this decision.

The formal decision from the DSMC will be communicated to the PI and the study team, as well as all HDFCCC Directors and Managers and the IRB of this decision. If this is an NCI-CTEP trial, then the NCI Program Director will be notified of this suspension on trial activities. If this is an Industry-Sponsored trial, then the Industry-Sponsor (i.e., Pharmaceutical company) will be notified of this suspension on trial activities. The study team will then complete the reporting form(s) to the IRB and update clinicaltrials.gov with this decision to suspend accrual.

The DSMC will work with the PI and the study team to ensure that all issues are resolved prior to the study team submitting a formal request to the DSMC to request that the mandatory suspension on enrollment be lifted.

After all issues have been satisfactorily resolved by the study team, the PI will request that the DSMC approve the removal of the accrual suspension (Appendix J). The DSMC will discuss this request at the next scheduled DSMC Meeting. After DSMC approval, the DSMC will communicate this approval to the CCCROC and the UCSF IRB and PRC, as well as the PI and study team, of this decision. Additionally, the NCI Program Director will be notified if this is a NCI-CTEP trial or the Industry-Sponsor will be notified if this is an Industry-Sponsored (i.e., Pharmaceutical trial) of this removal of accrual suspension. Once the study program accrual is resumed, the DSMC Manager and the

DSMC Chair will meet with the study program Lead CRC and/or PPM on a regular basis (i.e., every other week) to review accrual, staffing, issues encountered with the trials within the study program. These meetings will continue for 6-12 months until confirmation that all issues are resolved within the study program.

If the DSMC determines that there are unacceptable toxicities as a result of the study conduct by the PI and the study team, then the DSMC can permanently suspend the trial. If this occurs, then CCCROC, the UCSF IRB, PRC, the PI and the study team will be notified, as well as the NCI Program Director if this is a NCI-CTEP trial and the Industry-Sponsor if this is an Industry-Sponsored (i.e., Pharmaceutical trial).

## **VIII. Conflict of Interest**

The voting members of the DSMC (i.e., MDs) must step out from discussion during the DSMC meeting for any review of their trials in which they are the PI. If a monitoring visit report is from a trial in which the DSMC voting member is the PI, then the voting member must also recuse himself or herself from the discussion of this topic. Additionally, the DSMC Chair or Vice Chair cannot sign a Monitoring Visit Report (MVR) from a trial monitored/audited in the DSMC Chair or DSMC Vice Chair's Site Committee.

## **IX. Guidelines for Establishing and Operating a UCSF HDFCCC DSMB**

### **1. Membership**

- a. The HDFCCC DSMC Monitors will perform monitoring activities.
- b. Voting members of the DSMB will be the same voting members of the DSMC. Members should view themselves as representing the interest of patients and not that of the institution.

### **2. Meeting Procedures**

- a. Frequency
  - i. DSMB reports will be reviewed at the DSMC Meetings every six weeks.
- b. Elements for Review
  - i. A written summary of status, toxicity and outcomes of the clinical trial will be prepared by the study coordinator and reviewed by the principal

investigator and clinical trial statistician. The summary will be submitted to DSMB members allowing sufficient review time prior to meeting.

- ii. This summary will also address specific toxicity concerns as well as concerns about the conduct of the trial. It may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

### **3. Recommendations**

- a. It is the responsibility of the PI, the clinical trial statistician(s), and individual DSMB members to ensure that the DSMB is kept apprised of non-confidential results from other related studies that become available, and any programmatic concerns related to the clinical trial being monitored. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to the specific trial.
- b. DSMB recommendations will be given to the PI and Sponsor. The DSMB must provide an adequate rationale for recommendations made to change the trial for other than safety or efficacy reasons.
- c. The PI is responsible for implementing the change recommended by the DSMB as expeditiously as possible.
- d. If the PI does not agree with the DSMB recommendation, the sponsor must be informed of the reason for disagreement.
- e. The sponsor, DSMB Chair, and PI will be responsible for reaching a mutually acceptable decision about the study.

### **4. Release of Outcome Data**

- a. In general, outcome data should not be made available to individuals outside of the DSMB until accrual has been completed and all patients have completed study treatment
- b. The DSMB may approve the release of outcome data on a confidential basis to the PI for planning the preparation of manuscripts and/or to a small number of others for future trial planning purposes.
- c. Any release of outcome data prior to the DSMB recommendation for general dissemination of results must be reviewed and approved by the DSMB.

## **5. Confidentiality**

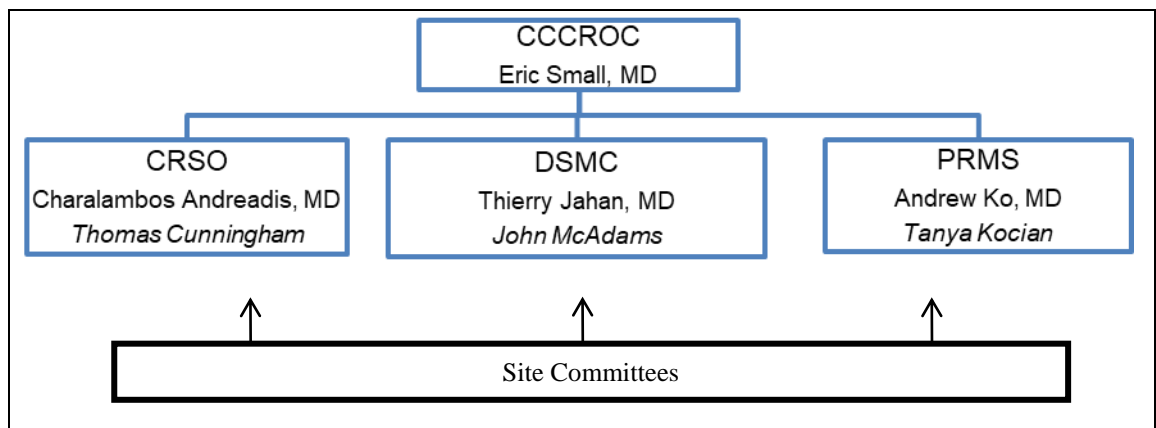
- a. No communication, either written or verbal, of the deliberations or recommendations of the DSMB will be made outside of the DSMB.
- b. Outcome results are strictly confidential and must not be divulged to any non-member until the recommendations to release the results are accepted and implemented.

## **6. Conflict of Interest**

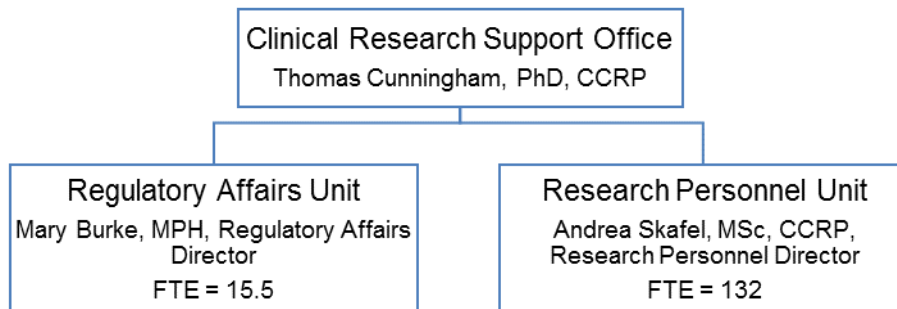
- a. DSMB members are subject to the UCSF policies regarding standards of conduct.
- b. Individuals invited to serve on the DSMB (voting or non-voting) will disclose any potential conflicts of interest, whether real or perceived, to the PI and the appropriate institutional officials, in accordance with the UCSF Conflict of Interest Policies. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest as described in 45 CFR Part 94.
- c. Decisions concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in the DSMB will be made in accordance with the UCSF Conflict of Interest Policies.
- d. Potential conflicts, which develop during a member's tenure on a DSMB, must also be disclosed and addressed in accordance with the UCSF Policies.



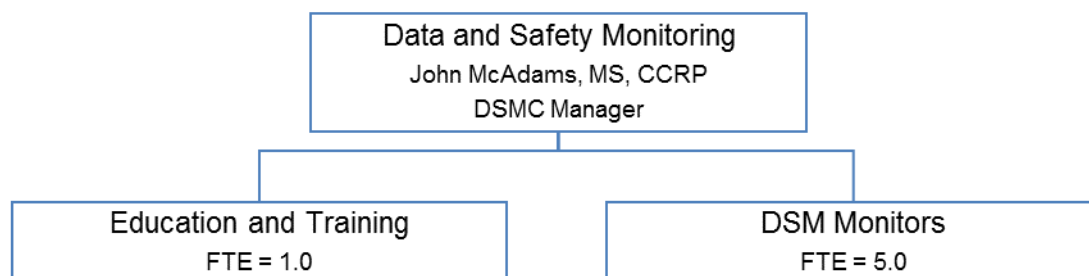
**Appendix A. HDFCCC Clinical Trials Infrastructure:** CCCROC coordinates the activities of the three units, each of which have a Faculty Director and a Staff Manager.



**Appendix B. Clinical Research Support Office:** *The two units of the CRSO, their staff directors, and personnel*



**Appendix C: DSM Organization:** *The two units of the DSM and their staff manager and personnel.*



## **Appendix D. UCSF HDFCCC Site Committees**

<u>Site Committee</u>	<u>Chair</u>
Breast Oncology	John Park, MD
Cancer Immunotherapeutics	Peter Sayre, MD
Cutaneous Oncology	Katy Tsai, MD
Developmental Therapeutics	Pamela Munster, MD
Gastrointestinal Oncology	Andrew Ko, MD
Genitourinary Oncology	Charles Ryan, MD
Gynecologic Oncology	Lee-May Chen, MD
Hematopoietic Oncology (Adult)	Thomas Martin, MD
Neurologic Oncology	Nicholas Butowski, MD
Oral, Head & Neck Oncology	Alain Algazi, MD
Pediatric Oncology	Annu Banerjee, MD
Radiation Oncology	Mary Feng, MD
Supportive Care	Chris Miaskowski RN, PhD
Thoracic Oncology	Matthew Gubens, MD

## **Appendix E. UCSF HDFCCC Data and Safety Monitoring Committee**

Thierry Jahan, MD	Chair and Thoracic Oncology
Andrew Ko, MD	Vice Chair and Gastrointestinal Oncology
Rahul Aggarwal, MD	Vice Chair and Genitourinary Oncology
Jennie Taylor, MD	Neurologic Oncology
Kristin Shimano, MD	Pediatric Oncology
Michelle Melisko, MD	Breast Oncology
Weiyun Ai, MD	Hematologic Oncology
Steve Braunstein, MD	Radiation Oncology
Joan Hilton, PhD	Biostatistics Core
Maha Kadafour, PharmD	Investigational Drug Service

### **Data and Safety Monitors/Education and Training Coordinator:**

John F. McAdams, MS, CCRP	Manager DSM
Bernadette Paolini, RN, CCRC	DSM Monitor
Maureen Lance, RN, CCRC	DSM Monitor
Fred Fishman, BS, CCRP	DSM Monitor
Marvin Bolanos, BS, CCRP	DSM Monitor
Amy Li, MPA	Education and Training Coordinator

## **Appendix F: PI Training Checklists**

UCSF ITR PI ONBOARDING CHECKLIST - Microsoft Word non-commercial use

UCSF Helen Diller Family Comprehensive Cancer Center UCSF ITR PI ONBOARDING CHECKLIST

Employee Name: \_\_\_\_\_ Start Date: \_\_\_\_\_

**New Hire Onboarding Requirements**

Training Topic	Completion Date	PI Initial	ETC/DSMC Manager Initial
Introduction to UCSF HDFCCC & ITR			
Department research staff & roles			
Introduction to UCSF clinical research data systems			
PI responsibilities for clinical trials <ul style="list-style-type: none"> <li>Protocol Review and Development Stage               <ul style="list-style-type: none"> <li>Trial activation process (site committee, PRC)</li> <li>CRC effort</li> <li>Sign off on final budget, calendar, and MCA</li> <li>IT/IST</li> <li>MCT</li> <li>Pharmacy orders</li> <li>1572, DOA</li> <li>SIV</li> <li>Cooperative group trials</li> </ul> </li> </ul>			
PI responsibilities for clinical trials <ul style="list-style-type: none"> <li>After study activation               <ul style="list-style-type: none"> <li>Consent process</li> <li>Screening window</li> <li>Eligibility criteria</li> <li>Enrollment</li> </ul> </li> </ul>			
PI responsibilities for clinical trials <ul style="list-style-type: none"> <li>Treatment phase               <ul style="list-style-type: none"> <li>Review patient orders</li> <li>Review, attribute, and sign labs</li> <li>Review, attribute, and sign scans</li> <li>Assess and grade AE</li> <li>Report SAEs within 24 hours</li> <li>One on one time with CRCs</li> </ul> </li> </ul>			
Meet with industry monitors <ul style="list-style-type: none"> <li>Financial information               <ul style="list-style-type: none"> <li>Post award analyst</li> <li>Monitor balance sheets</li> <li>Review and sign off on study charges</li> </ul> </li> </ul>			
PI responsibilities for clinical trials <ul style="list-style-type: none"> <li>Regulatory &amp; supervision               <ul style="list-style-type: none"> <li>Attend site committee</li> <li>Protocol and/or ICF amendments</li> <li>Verbal risk/reconsent</li> <li>Review internal/external safety reports</li> <li>Review DOA/1572 logs</li> <li>Attend multisite teleconference</li> <li>Respond to all emails in a timely manner</li> </ul> </li> </ul>			
Audit vs. Inspection <ul style="list-style-type: none"> <li>How to prepare</li> <li>Roles &amp; responsibilities</li> <li>DSMC role</li> </ul>			
Fair treatment of study staff <ul style="list-style-type: none"> <li>Understand study staff career goals</li> <li>How you can help them succeed</li> <li>Positive work environment</li> </ul>			

Please sign below to certify the completion of the UCSF ITR PI onboarding training requirements

Faculty Signature & Date	Education & Training Coordinator Signature & Date	DSMC Manager Signature & Date
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UCSF ITR ESTABLISHED PI TRAINING CHECKLIST - Microsoft Word non-commercial use

UCSF Helen Diller Family Comprehensive Cancer Center

UCSF ITR PI TRAINING CHECKLIST

Principal PI Name: \_\_\_\_\_ Start Date: \_\_\_\_\_

**Established PI Training Requirements**

Training Topic	Completion Date	PI Initial	ETC/DSMC Manager Initial
Introduction to UCSF HDCCC ITR			
Protocol Review and Monitoring System/ Protocol Review Committee			
Data and Safety Monitoring Committee			
Department research staff & roles <ul style="list-style-type: none"> <li>Safety Team</li> <li>Protocol Development Team</li> <li>Coverage Analyst &amp; Budget</li> <li>Research team staff</li> </ul>			
PI responsibilities for clinical trials <ul style="list-style-type: none"> <li>Protocol Review and Development Stage <ul style="list-style-type: none"> <li>Trial activation process (site committee, PRC)</li> <li>CRC effort</li> <li>Sign off on final budget, calendar, and MCA</li> <li>IT/IST</li> <li>MCT</li> <li>Pharmacy orders</li> <li>1572, DOA</li> <li>SIV</li> <li>Cooperative group trials</li> </ul> </li> </ul>			
PI responsibilities for clinical trials <ul style="list-style-type: none"> <li>After study activation <ul style="list-style-type: none"> <li>Consent process <ul style="list-style-type: none"> <li>Consenting non-English speaking subjects</li> <li>Telephone consent</li> </ul> </li> <li>Screening window</li> <li>Eligibility criteria</li> <li>Enrollment</li> </ul> </li> </ul>			
PI responsibilities for clinical trials			

1

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UCSF ITR ESTABLISHED PI TRAINING CHECKLIST - Microsoft Word non-commercial use

UCSF Helen Diller Family Comprehensive Cancer Center

UCSF ITR PI TRAINING CHECKLIST

<ul style="list-style-type: none"> <li>Treatment phase <ul style="list-style-type: none"> <li>Review patient orders</li> <li>Review, attribute, and sign labs</li> <li>Review, attribute, and sign scans</li> <li>Assess and grade AE</li> <li>Report SAEs within 24 hours</li> <li>One on one time with CRCs</li> <li>Meet with industry monitors</li> </ul> </li> </ul>			
PI responsibilities for clinical trials <ul style="list-style-type: none"> <li>Financial information <ul style="list-style-type: none"> <li>Post award analyst</li> <li>Monitor balance sheets</li> <li>Review and sign off on study charges</li> </ul> </li> </ul>			
PI responsibilities for clinical trials <ul style="list-style-type: none"> <li>Regulatory &amp; supervision <ul style="list-style-type: none"> <li>Attend site committee</li> <li>Protocol and/or ICF amendments</li> <li>Verbal risk/reconsent</li> <li>Review internal/external safety reports</li> <li>Review DOA/1572 logs</li> <li>Attend multisite teleconference</li> <li>Respond to all emails in a timely manner</li> </ul> </li> </ul>			
Emergency Use, Compassionate Use/Expanded Access			
Audit vs. Inspection <ul style="list-style-type: none"> <li>How to prepare</li> <li>Roles &amp; responsibilities</li> <li>DSMC role</li> </ul>			
Fair treatment of study staff <ul style="list-style-type: none"> <li>Understand study staff career goals</li> <li>How you can help them succeed</li> <li>Positive work environment</li> </ul>			

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UCSF ITR ESTABLISHED PI TRAINING CHECKLIST - Microsoft Word non-commercial use

UCSF Helen Diller Family Comprehensive Cancer Center

## UCSF ITR PI TRAINING CHECKLIST

Please sign below to certify the completion of the UCSF ITR PI onboarding training requirements

Faculty Signature & Date	Education & Training Coordinator Signature & Date	DSMC Manager Signature & Date
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## Appendix G. Data and Safety Monitoring Reports: Subject Report

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UCSF Helen Diller Family Comprehensive Cancer Center  
Data Safety Monitoring Report  
Subject Review

Study Title:  
CC #: UCSF IRB #: UCSF IRB Expiration Date:  
Research Group:  
Principal Investigator:  
CRC:  
Auditor:  
Site Visit Date:

Current study status: Total accrual to date: Total number of subjects reviewed: Type of visit:

Areas of Review	Assessments
<b>Study Management</b> a) The consent process is implemented per UCSF IRB application. b) The study has eligibility checklist that reflects the current protocol. c) Documentation of treatment and assessment was found. d) General quality of protocol was acceptable. e) Subject(s) were removed from study per protocol. f) General quality of data was satisfactory (CTMS). Phase I only: current Cohort DSMC approved dose escalation for last cohort. DLTs were identified in this cohort.	a) <input type="checkbox"/> Yes <input type="checkbox"/> No b) <input type="checkbox"/> Yes <input type="checkbox"/> No c) <input type="checkbox"/> Yes <input type="checkbox"/> No d) <input type="checkbox"/> Yes <input type="checkbox"/> No e) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A f) <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Toxicity documentation and management</b> a) Subjects were dosed correctly. b) Dose modifications per protocol.	a) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A b) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
<b>Comments regarding study management:</b>	
<b>The Consent Process:</b>	

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Report date:  
Subject Monitoring Form

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Data Safety Monitoring Report  
Subject Review

Subject ID # \_\_\_\_\_

Subject initials \_\_\_\_\_

Monitored from \_\_\_\_\_ to \_\_\_\_\_ Subject's Current Status: \_\_\_\_\_

a) Subject consented with correct ICF version by MD or nursing staff with all required signatures ☐ Yes ☐ No

b) Subject is entered into the CTMS with treatment status up to date. ☐ Yes ☐ No

c) Were all screening and pretreatment procedures done correctly? ☐ Yes ☐ No

d) Subject eligibility confirmed with supporting documentation and signed off. ☐ Yes ☐ No

e) Treatment per protocol confirmed. ☐ Yes ☐ No

f) All assessments completed per protocol. ☐ Yes ☐ No

g) AEs and SAEs entered in CTMS and confirmed by source documents. ☐ Yes ☐ No

h) Were new risks communicated with subjects as per Safety Reporting Policy? ☐ Yes ☐ No ☐ N/A

i) CTMS data: Are queries in OnCore? ☐ Yes ☐ No

j) Did any Protocol Violations or Consent Incidents occur? If yes: ☐ Yes ☐ No

k) Have all PV /Consent Incidents been reported per UCSF IRB guidelines? ☐ Yes ☐ No ☐ N/A

Comments regarding subject review:

Subject initials \_\_\_\_\_ Subject ID # \_\_\_\_\_

Monitored from \_\_\_\_\_ to \_\_\_\_\_ Subject's Current Status: \_\_\_\_\_

a) Subject consented with correct ICF version by MD or nursing staff with all required signatures ☐ Yes ☐ No

b) Subject is entered into the CTMS with treatment status up to date. ☐ Yes ☐ No

c) Were all screening and pretreatment procedures done correctly? ☐ Yes ☐ No

d) Subject eligibility confirmed with supporting documentation and signed off. ☐ Yes ☐ No

CC#: \_\_\_\_\_ Page 2  
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Data Safety Monitoring Report  
Subject Review

<p>e) Treatment per protocol confirmed.</p> <p>f) All assessments completed per protocol, including CT/MRI.</p> <p>g) AEs and SAEs entered in CTMS and confirmed by source documents.</p> <p>h) Were new risks were communicated with subjects as per Safety Reporting Policy?</p> <p>i) CTMS data: Are queries in OnCore?</p> <p>j) Did any Protocol Violations or Consent Incidents occur? If yes:</p> <p>k) Have all PV /Consent Incidents been reported per UCSF IRB guidelines?</p>	<p>e) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>f) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>g) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>h) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p>i) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>j) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>k) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>
<p><b>Comments regarding subject review:</b></p>	
<p>Subject initials ____ Subject ID # ____</p> <p>Monitored from ____ to ____ Subject's Current Status: ____</p> <p>a) Subject consented with correct ICF version by MD or nursing staff with all required signatures</p> <p>b) Subject is entered into the CTMS with treatment status up to date.</p> <p>c) Were all screening and pretreatment procedures done correctly?</p> <p>d) Subject eligibility confirmed with supporting documentation and signed off.</p> <p>e) Treatment per protocol confirmed.</p> <p>f) All assessments completed per protocol, including CT/MRI.</p> <p>g) AEs and SAEs entered in CTMS and confirmed by source documents.</p> <p>h) Were new risks were communicated with subjects as per Safety Reporting Policy?</p> <p>i) CTMS data: Are queries in OnCore?</p> <p>j) Did any Protocol Violations or Consent Incidents occur? If yes:</p> <p>k) Have all PV /Consent Incidents been reported per UCSF IRB guidelines?</p>	<p>a) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>b) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>c) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>d) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>e) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>f) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>g) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>h) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p>i) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>j) <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>k) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>
<p><b>Comments regarding subject review:</b></p>	

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Data Safety Monitoring Report  
Subject Review

Subject initials \_\_\_\_ Subject ID # \_\_\_\_  
Monitored from \_\_\_\_ to \_\_\_\_ Subject's Current Status: \_\_\_\_

a) Subject consented with correct ICF version by MD or nursing staff with all required signatures a) ☐ Yes ☐ No

b) Subject is entered into the CTMS with treatment status up to date. b) ☐ Yes ☐ No

c) Were all screening and pretreatment procedures done correctly? c) ☐ Yes ☐ No

d) Subject eligibility confirmed with supporting documentation and signed off. d) ☐ Yes ☐ No

e) Treatment per protocol confirmed. e) ☐ Yes ☐ No ☐ N/A

f) All assessments completed per protocol. f) ☐ Yes ☐ No

g) AEs and SAEs entered in CTMS and confirmed by source documents. g) ☐ Yes ☐ No

h) Were new risks were communicated with subjects as per Safety Reporting Policy? h) ☐ Yes ☐ No ☐ N/A

i) CTMS data: Are queries in OnCore? i) ☐ Yes ☐ No

j) Did any Protocol Violations or Consent Incidents occur? If yes: j) ☐ Yes ☐ No

k) Have all PV /Consent Incidents been reported per UCSF IRB guidelines? k) ☐ Yes ☐ No ☐ N/A

Comments regarding subject review:

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**G. Overall Summary Evaluation of Visit:**

☐ Satisfactory

☐ Acceptable with follow-up items to be completed by the following date \_\_\_\_\_

☐ Significant findings with follow-up response to DSMC required

☐ Unsatisfactory, halt enrollment of new subjects, corrective action plan required within 10 days to the DSMC. The HDFCCC DSMC Chair will notify the CHR regarding the results of this audit/monitoring visit

\_\_\_\_\_  
Auditor's Signature Date \_\_\_\_\_

Reviewed by:  
John F. McAdams, MS, CCRP  
Manager, DSMC

\_\_\_\_\_  
Signature Date \_\_\_\_\_

Approval:  
Thierry Jahan, MD  
Chair, DSMC

\_\_\_\_\_  
Signature Date \_\_\_\_\_

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## Appendix H. Data and Safety Monitoring Reports: Regulatory Report

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Data Safety Monitoring Report  
Regulatory Review

Study Title: \_\_\_\_\_ UCSF IRB Approval #: \_\_\_\_\_  
CC #: \_\_\_\_\_ UCSF IRB Expiration Date: \_\_\_\_\_  
Research Group: \_\_\_\_\_  
Principal Investigator: \_\_\_\_\_  
Regulatory CRC: \_\_\_\_\_  
Auditor: \_\_\_\_\_ Site Visit Date: \_\_\_\_\_

Areas of Review	Assessments
<b>Protocol</b>	
a. Is the current IRIS approved protocol attached in IRIS or filed in a zip drive?	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
b. Have all protocol signature pages been signed and dated by the PI (filed in OnCore or in a zip drive)?	b. <input type="checkbox"/> Yes <input type="checkbox"/> No
c. Are all prior UCSF IRB approved protocol attached in IRIS or filed in a zip drive?	c. <input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Consent</b>	
a. Is the current stamped version of the ICF filed in IRIS or filed in a zip drive?	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
b. Are all prior UCSF IRB approved version ICFs filed in IRIS or filed in a zip drive?	b. <input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Investigator Brochure</b>	
a. Is the current IB filed in IRIS or filed in a zip drive?	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
b. Are all prior IB approved versions filed in IRIS or filed in a zip drive?	b. <input type="checkbox"/> Yes <input type="checkbox"/> No
c. If commercial, is the package insert on file attached in OnCore or filed in a zip drive?	c. <input type="checkbox"/> Yes <input type="checkbox"/> No
d. Is there IRIS documentation of submission on file with acknowledgement/approval?	d. <input type="checkbox"/> Yes <input type="checkbox"/> No
e. Timely UCSF IRB submission of IBs?	e. <input type="checkbox"/> Yes <input type="checkbox"/> No
<b>IND/IDE Application and FDA Approval</b>	

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Program: \_\_\_\_\_ Regulatory MVR  
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**UCSF Helen Diller Family Comprehensive Cancer Center  
Data Safety Monitoring Report  
Regulatory Review**

<p>a. Is the initial application on file in OnCore or filed in a zip drive?</p> <p>b. Was the FDA Confirmation Letter of IND Status submitted to UCSF IRB (for studies where the PI holds the IND)?</p> <p>c. Was the first patient enrolled more than 30 days after receiving FDA confirmation letter?</p>	<p>a. <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>b. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p>c. <input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p><b>IND Status:</b> <input type="checkbox"/> PI Held IND <input type="checkbox"/> Exempt</p> <p>a. When PI holds the IND, have the IND Annual Reports been filed as required with the FDA? (filed in OnCore or on a zip drive) (If exempt, not applicable).</p>	<p>a. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>
<b>PRC Approvals</b>	
<p>a. Did the PRC approvals precede the UCSF IRB approvals?</p> <p>b. PRC approved Protocol Versions are documented in OnCore?</p> <p>c. PRC amendment with Protocol and SOC is documented in OnCore under detail section?</p>	<p>a. <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>b. <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>c. <input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<b>UCSF IRB Approvals</b>	
<p>a. Any lapses in UCSF IRB approval? If yes, where any patients enrolled?</p> <p>b. iRIS approvals on file in iRIS or filed in a zip drive for initial submission?</p> <p>c. iRIS approvals on file in iRIS or filed in a zip drive for all modifications and continuing annual renewals?</p> <p>d. Per ITR policy, if Administrative <u>Memo</u>,  <ul style="list-style-type: none"> <li>▪ If for safety, was protocol amended and approved within 60 days?</li> <li>▪ If for minor, allowed at time of next scheduled</li> </ul> </p>	<p>a. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p>b. <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>c. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p>d. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>

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UCSF Helen Diller Family Comprehensive Cancer Center Data Safety Monitoring Report Regulatory Review	
<p>amendment?</p> <ul style="list-style-type: none"> <li>PI has option of <u>not</u> submitting amendment if able to provide a determination/rationale that is acceptable to both CHR and DSMC?</li> </ul> <p>e. If PI holds the IND, were the FDA confirmations letters submitted to the UCSF IRB and is the IND number on the front of the cover page? ? Are these letters on file in OnCore or filed in a zip drive?</p> <p>f. If multicenter trial: are participating site's IRB approvals on file in OnCore or filed in a zip drive?</p> <p>g. If multicenter trial, are the key study personnel who can consent on file in IRIS under application for both coordinating site and participating site*?</p> <p>*As per participating site's IRB requirements.</p>	<p>e. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p>f. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p>g. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>
<p><b>Other Approvals</b></p> <p>Documentation of the following found in OnCore:</p> <p>a). Biosafety Committee (vaccines)?</p> <p>b). Radiation Committee?</p>	
<p>a. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p> <p>b. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A</p>	
<p>CC#: _____ Page 3</p> <p>Program: _____ Regulatory MVR</p> <p>Report date: _____ Version 6.0, 01Sep2016</p>	

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Data Safety Monitoring Report  
Regulatory Review

<b>SAE Section</b>	
a. SAE reports to the UCSF IRB with supporting - documentation (in IRIS or filed in a zip drive)?	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
b. SAE report to Sponsor with supporting documentation/e-mails (in OnCore or filed in a zip drive)?	b. <input type="checkbox"/> Yes <input type="checkbox"/> No
c. In a Multicenter trial, did the coordinating site communicate new risks from the SAEs to the participating site(s) in teleconference minutes? (in OnCore or filed in a zip drive)?	c. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
d. In a Multicenter trial, are the participating site(s) submitting SAEs to the coordinating site as per protocol?	d. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
e. When PI holds the IND, were MedWatch forms (with supporting -documentation) submitted per timeline (filed in OnCore or on a zip drive)?	e. <input type="checkbox"/> Yes <input type="checkbox"/> No
f.	
<b>Protocol Violations and/or Incident Reports</b>	
a. PVs reported to UCSF IRB per their guidelines and timelines with supporting documentation?	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Correspondence</b>	
a. Was all correspondence to and from the Sponsor, other sites (for multicenter trials), etc, filed in OnCore or filed in a zip drive?	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Study Personnel</b>	
a. Coordinator training: (UCSF IRB, CITI, etc.) (filed in OnCore or filed in a zip drive).	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
b. Staff delegation log (filed in Regulatory Binder, OnCore or filed in a zip drive).	b. <input type="checkbox"/> Yes <input type="checkbox"/> No
c. CVs for all investigators (filed in OnCore or filed in a zip drive).	c. <input type="checkbox"/> Yes <input type="checkbox"/> No
d.	d. <input type="checkbox"/> Yes <input type="checkbox"/> No

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UCSF Helen Diller Family Comprehensive Cancer Center  
Data Safety Monitoring Report  
Regulatory Review

d. MD licenses (filed in OnCore or filed in a zip drive).	
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**FDA Forms 1571/1572**

a. Has the Form FDA 1571 and FDA 1572 (for ISTs where the PI holds the IND) or Form 1572 (for ISTs where the PI does not hold the IND or Sponsored trials) been completed and signed/dated by the PI (filed in OnCore or in a zip drive)?	a. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
b. Was the Form 1572 updated for staff or lab changes as applicable (filed in OnCore or in a zip drive)?	b. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A

**Other Documents**

a. PI review and signature/date of Weekly and/or Monthly AE review (Phase 1 – weekly review, Phase 2- monthly review) (filed in OnCore or filed in a zip drive).	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
b. OnCore Case Report Form (CRF) completion guidelines (filed in OnCore or filed in a zip drive)?	b. <input type="checkbox"/> Yes <input type="checkbox"/> No
c. Site Committee Meeting Minutes (filed in OnCore or field in a zip drive)?	c. <input type="checkbox"/> Yes <input type="checkbox"/> No

CONFIDENTIAL

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Program: \_\_\_\_\_ Regulatory MVR  
Report date: \_\_\_\_\_ Version 6.0, 01Sep2016

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UCSF Helen Diller Family Comprehensive Cancer Center  
Data Safety Monitoring Report  
Regulatory Review

<b>New Risks</b>	
a) IND Safety Office: Reviewed zip drive of Electronic Safety reports (i.e., IBs, External Safety reports and Safety letters) and electronic PI signatures?	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
b) Were any new risk(s) identified by PI from IBs, External SAEs, Internal SAEs, and Safety Letters?	b. <input type="checkbox"/> Yes <input type="checkbox"/> No
▪ If yes, were these new risk (s) reviewed by the PI in timely manner per ITR safety policy?	<input type="checkbox"/> Yes <input type="checkbox"/> No
▪ Were these new risks reported to UCSF IRB/ IRIS in timely manner?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Screening and Enrollment Log</b>	
a. Is there a Screening and Enrollment Log filed in <b>OnCore</b> or <b>filed in a zip drive</b> ?	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Labs</b>	
a. Are the CLIA certifications ( <b>filed in OnCore</b> or <b>filed in a zip drive</b> )?	a. <input type="checkbox"/> Yes <input type="checkbox"/> No
b. Are the CAPs ( <b>filed in OnCore</b> or <b>filed in a zip drive</b> )?	b. <input type="checkbox"/> Yes <input type="checkbox"/> No
c. Are the lab licenses ( <b>filed in OnCore</b> or <b>filed in a zip drive</b> )?	c. <input type="checkbox"/> Yes <input type="checkbox"/> No
d. Are the laboratory normal references ( <b>filed in OnCore</b> or <b>filed in a zip drive</b> )?	d. <input type="checkbox"/> Yes <input type="checkbox"/> No
e. Is the CV of the Lab Director ( <b>filed in OnCore</b> or <b>filed in a zip drive</b> )?	e. <input type="checkbox"/> Yes <input type="checkbox"/> No

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UCSF Helen Diller Family Comprehensive Cancer Center  
Data Safety Monitoring Report  
Regulatory Review

Comments:

G. Overall Summary:

☐ Satisfactory

☐ Acceptable with follow-up items to be completed by the following date \_\_\_\_\_.

☐ Significant findings with follow-up response to DSMC required

☐ Unsatisfactory, halt enrollment of new subjects, corrective action plan required within 10 days to the DSMC. The HDFCCC DSMC Chair will notify the CHR regarding the results of this audit/monitoring visit

Auditor's Signature \_\_\_\_\_ Date \_\_\_\_\_

Reviewed by:  
John F. McAdams, MS, CCRP  
Manager, DSMC

Signature \_\_\_\_\_ Date \_\_\_\_\_

Approval:  
Thierry Jahan, MD  
Chair, DSMC

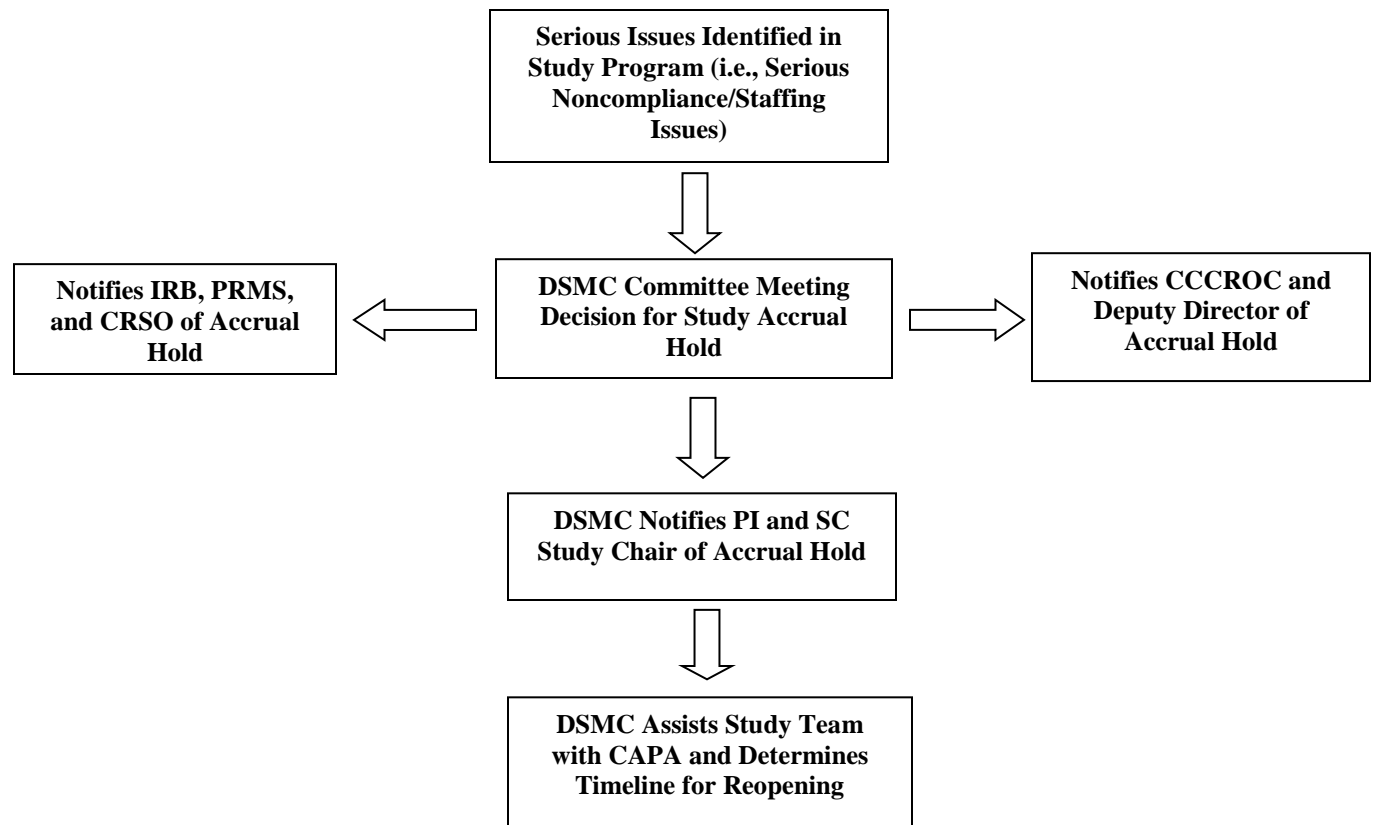
Signature \_\_\_\_\_ Date \_\_\_\_\_

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Program: \_\_\_\_\_ Regulatory MVR  
Report date: \_\_\_\_\_ Version 6.0, 01Sep2016

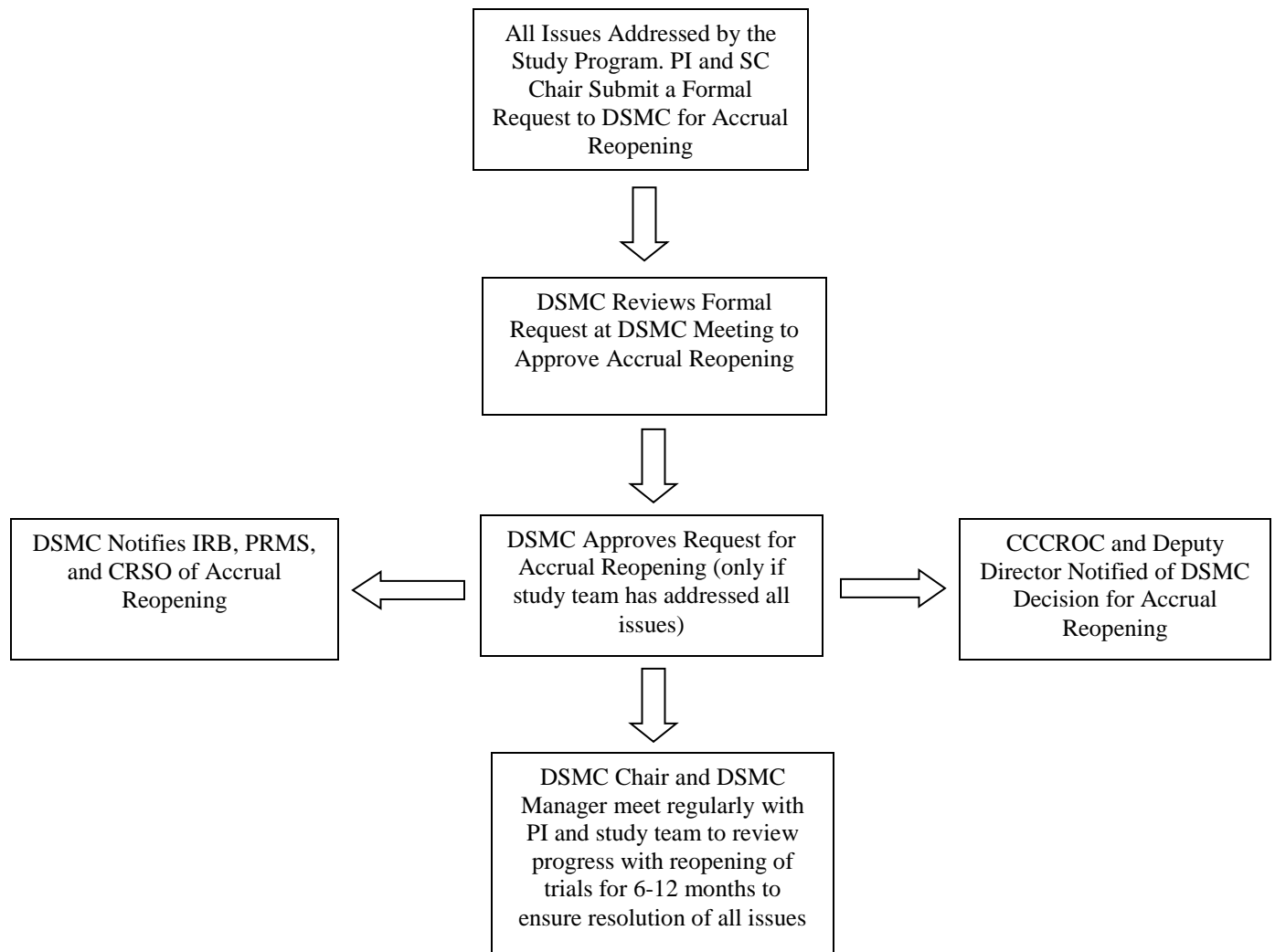
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## **Appendix I: DSMC Remediation Process: Study Program Accrual Hold**



## **Appendix J: DSMC Remediation Process: Study Program Accrual Reopening**



## **Appendix K. Model DSMP Templates for Investigators to Insert into Protocols**

**Note to Investigators:** These plans are templates for your funding applications and for your protocol preparation.

Please contact the DSMC for updated templates.



## **Appendix K.1 (Single Site)**

### **Data and Safety Monitoring Plan for a Phase I Dose Escalation Institutional Study**

#### **1. Oversight and Monitoring Plan**

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data in each cohort.
- Review of serious adverse events.
- Approval of dose escalation by DSMC Chair, or Vice Chair.
- Real-time monitoring (depending on study accrual).
- Minimum of a yearly regulatory audit.

#### **2. Monitoring and Reporting Guidelines**

Investigators will conduct continuous review of data and patient safety and discuss each patient's treatment at weekly site committee meetings. The discussions are documented in the site committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

All institutional Phase I therapeutic studies are designated with a high-risk assessment (see Appendix H). The data for each patient is monitored by a DSMC monitor in real time as patients are enrolled and includes all visits through the first post-Dose Limiting Toxicity (DLT) visit.

#### **3. Review and Oversight Requirements**

### 3.1 Adverse Event Monitoring

All clinically significant adverse events (AEs), whether or not considered expected or unexpected and whether or not considered associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All clinically significant adverse events entered into OnCore® will be reviewed on a weekly basis at the site committee meetings. The site committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

### 3.2 Serious Adverse Event Reporting

By definition, an Adverse Event is defined as a Serious Adverse Event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.

- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution

Serious Adverse Event reporting will be in accordance with all UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

<https://irb.ucsf.edu/adverse-event>

FDA website for guidance in reporting serious adverse events:

[www.fda.gov/Safety/MedWatch/HowToReport/default.htm](http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)

Med Watch forms and information:

[www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm)

All Serious Adverse Events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meetings, which take place every six (6) weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study, or within 30 days after the last administration of the study drug(s), and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Principal Investigator or his/her designee must notify the DSMC Chair or his qualified alternate within 1 business day.

The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication, via e-mail, with a copy of the e-mail sent to the DSMC Manager.

### **3.3 Dose Escalations**

At the time of dose escalation, a written report will be submitted to the DSMC Chair (or Vice Chair) describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting Toxicities (DLTs) observed, in accordance with the protocol. The report

will be reviewed by the DSMC Chair or Vice Chair and written authorization to proceed or a request for more information will be issued within two business days of the request. The report is then reviewed at the subsequent DSMC meeting. In the event that the committee does not concur with the DSMC Chair's decision, study accrual is held while further investigation takes place.

### **3.4 Review of Adverse Event Rates**

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. and the IRB must be notified within 10 business days via an iRIS Reporting Form.

#### **Data and Safety Monitoring Committee Contacts:**

Thierry Jahan, MD (DSMC  
Chair)  
415-885-3792  
Thierry.jahan@ucsf.edu  
Box 1705  
UCSF HDFCCC  
San Francisco, CA 94158

DSMC Monitors  
Box 0128  
UCSF HDFCCC  
San Francisco, CA 94143

## **Appendix K.2 (Single Site)**

### **Data and Safety Monitoring Plan for a High Risk Vaccine or Gene-Therapy Institutional Study**

#### **1. Oversight and Monitoring Plan**

The UCSF Helen Diller Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of all patient data.
- Review of serious adverse events.
- Real-time monitoring (depending on study accrual)
- Minimum of a yearly regulatory audit

#### **2. Monitoring and Reporting Guidelines**

Investigators will conduct continuous review of data and patient safety at weekly site committee meetings where the results of each patient's treatment are discussed and documented in the site committee minutes. The discussion will include the number of patients, significant toxicities as described in the protocol and observed responses.

All institutional vaccine or gene therapy therapeutic studies are deemed with a high-risk assessment (see Appendix H). The data is monitored by a DSMC Monitor in real-time as patients are enrolled in the trial through the first cycle of study drug therapy. All patients enrolled in the trial are monitored through the first cycle of therapy.

#### **3. Review and Oversight Requirements**

##### **3.1 Adverse Event Monitoring**

All clinically significant adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All adverse events entered into OnCore® will be reviewed on a weekly basis at the site committee meetings. The site committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

### 3.2 Serious Adverse Event Reporting

By definition, an Adverse Event is defined as a Serious Adverse Event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

<https://irb.ucsf.edu/adverse-event>

FDA website for guidance in reporting serious adverse events:

[www.fda.gov/Safety/MedWatch/HowToReport/default.htm](http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)

Med Watch forms and information:

[www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm)

All Serious Adverse Events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meetings, which take place every six (6) weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Investigator or his/her designee must notify the DSMC Chair or Vice Chair within 1 business day.

The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail sent to the DSMC Manager.

### **3.3 Review of Adverse Event Rates**

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC at the time the increased rate is identified. The report will indicate if the incident of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail and the IRB must be notified via an iRIS Reporting Form.

### **Data and Safety Monitoring Committee Contacts:**

:

Thierry Jahan, MD (DSMC Chair)  
415-885-3792  
Thierry.jahan@ucsf.edu  
Box 1705  
UCSF HDFCCC  
San Francisco, CA 94158

DSMC Monitors  
Box 0128  
UCSF HDFCCC  
San Francisco, CA  
94143



## **Appendix K.3 (Single Site)**

### **Data and Safety Monitoring Plan for a Phase II or III Institutional Study**

#### **1. Oversight and Monitoring Plan**

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data.
- Review of serious adverse events.
- Auditing every six months (depending on study accrual).
- Minimum of a yearly regulatory audit.

#### **2. Monitoring and Reporting Guidelines**

Investigators will conduct continuous review of data and patient safety and discuss each patient's treatment at monthly site committee meetings. These discussions are documented in the site committee meeting minutes. The discussion will include the number of patients, significant toxicities in accordance with the protocol, and observed responses.

All institutional Phase II and III studies are designated with a moderate risk assessment (see Appendix H). The data is audited twice per year with twenty percent of the patients monitored (or at least three patients if the calculated value is less than three).

#### **3. Review and Oversight Requirements**

##### **3.1 Adverse Event Monitoring**

All Grade 3-5 Adverse Events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

### 3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Permanent or significant disability/incapacity
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

<https://irb.ucsf.edu/adverse-event>

FDA website for guidance in reporting serious adverse events:

[www.fda.gov/Safety/MedWatch/HowToReport/default.htm](http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)

Med Watch forms and information:

[www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm)

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iMedRIS®. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair or Vice Chair within 1 business day.

The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

### **3.3 Review of Adverse Event Rates**

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. and the IRB must be notified within 10 business days via an iRIS Reporting Form.

### **Data and Safety Monitoring Committee Contacts:**

Thierry Jahan, MD  
415-885-3792  
Thierry.jahan@ucsf.edu  
Box 1705  
UCSF HDFCCC  
San Francisco, CA 94158

DSMC Monitors  
Box 0128  
UCSF HDFCCC  
San Francisco, CA 94143

## **Appendix K.4 (Single Site)**

### **Data and Safety Monitoring Plan for a Nontherapeutic Institutional Study**

#### **1. Oversight and Monitoring Plan**

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data.
- Review of serious adverse events.
- Auditing on a yearly basis.
- Minimum of a yearly regulatory audit.

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for subject safety for all HDFCCC institutional clinical studies. Nontherapeutic studies are characterized as low risk studies due to the study design, as there isn't administration of drugs or complementary therapy that put the patient at significant risk. Twenty percent of all enrolled subjects will be audited once per year.

#### **2. Monitoring and Reporting Guidelines**

Investigators will conduct continuous review of data and patient safety at monthly Site Committee meetings. The risk assessment for this type of trial is low; hence, the study would be audited only once per year, with 20 percent of the enrolled subject being selected for audit.

#### **3. Review and Oversight Requirements**

##### **3.1 Adverse Event Monitoring**

All clinically significant adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All clinically significant adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings

### 3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

<https://irb.ucsf.edu/adverse-event>

FDA website for guidance in reporting serious adverse events:

[www.fda.gov/Safety/MedWatch/HowToReport/default.htm](http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)

Med Watch forms and information:

[www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm)

All Serious Adverse Events are entered into OnCore®, as well as submitted to the IRB via iRIS®. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six (6) weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Investigator or his/her designee must notify the DSMC Chair or Vice Chair within 1 business day. The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

### **3.3 Review of Adverse Event Rates**

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day and the IRB must be notified within 10 business days.

### **Data and Safety Monitoring Committee Contacts:**

Thierry Jahan, MD  
415-885-3792  
Thierry.jahan@ucsf.edu  
Box 1705  
UCSF HDFCCC  
San Francisco, CA 94158

DSMC Monitors  
Box 0128  
UCSF HDFCCC  
San Francisco, CA 94143



## **Appendix K.5 (Multicenter)**

### **Data and Safety Monitoring Plan for a Non-Therapeutic Multicenter Institutional Study**

#### **1. Oversight and Monitoring Plan**

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDF CCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data.
- Review of serious adverse events.
- Auditing on a yearly basis.
- Minimum of a yearly regulatory audit.

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for subject safety for all HDFCCC institutional clinical studies. Nontherapeutic studies are characterized as low risk studies due to the study design, as there is not administration of drugs or complementary therapy that put the patient at significant risk. Twenty percent of all enrolled subjects will be audited once per year.

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and patient safety and discuss each patient's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

#### **2. Multicenter communication**

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.

- Adverse Events (i.e., new adverse events and updates on unresolved adverse events and new safety information).
- Protocol Violations.
- Other issues affecting the conduct of the study.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites as per the study-specific guidelines listed in Appendix H. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and FDA regulations.

### 3 Review and Oversight Requirements

#### 3.1 Adverse Event Monitoring

All Grade 3-5 Adverse Events (AEs), regardless of being unexpected or considered to be associated with the use of the study drug will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse Events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating

Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled monthly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

### **3.2 Serious Adverse Event Reporting**

By definition, an Adverse Event is defined as a Serious Adverse Event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

<https://irb.ucsf.edu/adverse-event>

FDA website for guidance in reporting serious adverse events:

[www.fda.gov/Safety/MedWatch/HowToReport/default.htm](http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)

Med Watch forms and information:

[www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm)

All Serious Adverse Events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be

reported to the UCSF Coordinating Center within 1-business day of becoming aware of the event. The SAEs are reviewed and monitored by the UCSF Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

### **3.3 Review of Adverse Event Rates**

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day and the IRB must be notified within 10 business days via an iRIS Reporting Form.

### **Data and Safety Monitoring Committee Contacts:**

Thierry Jahan, MD (DSMC Chair)  
415-885-3792  
Thierry.jahan@ucsf.edu  
Box 1705  
UCSF HDFCCC  
San Francisco, CA 94158

DSMC Monitors  
Box 0128  
UCSF HDFCCC  
San Francisco, CA 94143

## **Appendix K.6 (Multicenter)**

### **Data and Safety Monitoring Plan for a Multicenter Institutional Study (Phase 1 Dose Escalation)**

#### **1. Oversight and Monitoring Plan**

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data in each cohort.
- Review of serious adverse events.
- Approval of dose escalation by DSMC Chair or Vice Chair.
- Real time monitoring (depending on study accrual).
- Minimum of a yearly regulatory audit.

#### **2. Monitoring and Reporting Guidelines**

All institutional Phase I therapeutic studies are designated with a high risk assessment (see Appendix H). The data is monitored by a DSMC monitor once a month as patients are enrolled and includes all visits through the first post-Dose Limiting Toxicity (DLT) period. At the time of dose escalation, a written report will be submitted to the DSMC Chair outlining the cohort dose, all adverse events and serious adverse event reports, and any Dose Limiting Toxicity as described in the protocol. The report will be reviewed by the DSMC Chair or qualified alternate and written authorization to proceed or a request for more information will be issued within two business days of the request. The report is then reviewed at the subsequent DSMC meeting. In the event that the committee does not concur with the DSMC Chair's decision, further study accrual is held while further investigation takes place.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and patient safety and discuss each patient's treatment at weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

#### **Multicenter communication**

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF

Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.
- Cohort updates (i.e., DLTs).
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information).
- Protocol violations.
- Other issues affecting the conduct of the study.

### **Dose Level Considerations**

The PI/Study Chair, participating investigators, and research coordinators from each site will review enrollment for each dose level cohort during the regularly scheduled conference calls. The dose level for ongoing enrollment will be confirmed for each patient scheduled to be enrolled at a site. Dose level assignments for any patient scheduled to begin treatment must be confirmed by the UCSF Coordinating Center via e-mail.

If a Dose Limiting Toxicity (DLT) arises in a patient treated at a participating site, all sites must be notified immediately by the UCSF Coordinating Center. The Study Chair has 1 business day (after first becoming aware of the event at either the UCSF Coordinating Center or the participating site) in which to report the information to all participating sites. If the DLT occurs at a participating site, the local investigator must report it to the UCSF Coordinating Center within one business day, after which the UCSF Coordinating Center will notify the other participating sites.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites as per the study-specific guidelines listed in Appendix H. The data (i.e., redacted copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and FDA guidelines.

## **3. Review and Oversight Requirements**

### **3.1 Adverse Event Monitoring**

All clinically significant adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse Events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All adverse events entered into OnCore® will be reviewed on a weekly basis at the UCSF Coordinating Center's Site Committee. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 1 business days of becoming aware of the event. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

### 3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.



- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

<https://irb.ucsf.edu/adverse-event>

FDA website for guidance in reporting serious adverse events:

[www.fda.gov/Safety/MedWatch/HowToReport/default.htm](http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)

Med Watch forms and information:

[www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm)

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within 10 business days of becoming aware of the event or during the next scheduled conference call, whichever is sooner. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The reporting procedure is by communication via e-mail, with a copy of the e-mail to the DSMC Manager.

### **3.3 Review of Adverse Event Rates**

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events

observed in the study is above the range stated in the Investigator's Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail and the IRB must be notified via 10 business days via an iRIS Reporting Form.

**Data and Safety Monitoring Committee Contacts:**

Thierry Jahan, MD (DSMC Chair)  
415-885-3792  
Thierry.jahan@ucsf.edu  
Box 1705  
UCSF HDFCCC  
San Francisco, CA 94158

DSMC Monitors  
Box 0128  
UCSF HDFCCC  
San Francisco, CA  
94143

## **Appendix K.7 (Multicenter)**

### **Data Safety Monitoring Plan for Vaccine or Gene Therapy Multicenter Study**

#### **1. Oversight and Monitoring Plan**

The UCSF-Helen Diller Family Comprehensive Cancer Center (HDF CCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDF CCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of all patient data.
- Review of serious adverse events.
- Real time monitoring (depending on study accrual).
- Minimum of a yearly regulatory audit.

#### **2. Monitoring and Reporting Guidelines**

All institutional vaccine or gene therapy therapeutic studies are designated with a high-risk assessment (see Appendix H). The data is monitored by a DSMC Monitor in real-time as patients are enrolled in the trial through the first cycle of study drug therapy. All patients enrolled in the trial are monitored through the first cycle of therapy.

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and patient safety and discuss each patient's treatment at weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

#### **Multicenter communication**

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.
- Adverse Events (i.e., new adverse events and updates on unresolved adverse events and new safety information).
- Protocol Violations.
- Other issues affecting the conduct of the study.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites as per the study-specific guidelines listed in Appendix H. The data (i.e., redacted copies of source documents) from the participating sites will be downloaded into the PC module of OnCore® prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and FDA guidelines.

### 3. Review and Oversight Requirement

#### 3.1 Adverse Event Monitoring

All clinically significant adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse Events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All adverse events entered into OnCore® will be reviewed on a weekly basis at the UCSF Coordinating Center Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled monthly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

### **3.2 Serious Adverse Event Reporting**

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

<https://irb.ucsf.edu/adverse-event>

FDA website for guidance in reporting serious adverse events:

[www.fda.gov/Safety/MedWatch/HowToReport/default.htm](http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)

Med Watch forms and information:

[www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm)

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB) guidelines via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within 1 business days of becoming aware of the event. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

### **3.3 Review of Adverse Event Rates**

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail and the IRB must be notified within 10 business days via an iRIS Reporting Form.

### **Data and Safety Monitoring Committee Contacts:**

Thierry Jahan, MD  
415-885-3792  
Thierry.jahan@ucsf.edu  
Box 1705  
UCSF HDFCCC  
San Francisco, CA 94158

DSMC Monitors  
Box 0128  
UCSF HDFCCC  
San Francisco, CA 94143

## **Appendix K.8 (Multicenter)**

### **Data and Safety Monitoring Plan for a Multicenter Study (Phase II or III study)**

#### **1. Oversight and Monitoring Plan**

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDF CCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data.
- Review of serious adverse events.
- Monitoring every six months (depending on patient accrual).
- Minimum of a yearly regulatory audit.

#### **2. Monitoring and Reporting Guidelines**

All institutional Phase II or III therapeutic studies are designated with a moderate risk assessment (see Appendix H). The data is monitored by a DSMC Monitor twice per year with twenty percent of the patients monitored (or at least three patients if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and patient safety and discuss each patient's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

#### **Multicenter communication**

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:



- Enrollment information.
- Adverse Events (i.e., new adverse events and updates on unresolved adverse events and new safety information).
- Protocol Violations.
- Other issues affecting the conduct of the study.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites as per the study-specific guidelines listed in Appendix H. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and FDA regulations.

### 3 Review and Oversight Requirements

#### 3.1 Adverse Event Monitoring

All Grade 3-5 Adverse Events (AEs), regardless of being unexpected or considered to be associated with the use of the study drug will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse Events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled monthly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

### **3.2 Serious Adverse Event Reporting**

By definition, an Adverse Event is defined as a Serious Adverse Event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

<https://irb.ucsf.edu/adverse-event>

FDA website for guidance in reporting serious adverse events:

[www.fda.gov/Safety/MedWatch/HowToReport/default.htm](http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm)

Med Watch forms and information:

[www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm)

All Serious Adverse Events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within 1 business days of becoming aware of the event. The SAEs are reviewed and monitored by the UCSF Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

### **3.3 Review of Adverse Event Rates**

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day and the IRB must be notified within 10 business days via an iRIS Reporting Form.

### **Data and Safety Monitoring Committee Contacts:**

Thierry Jahan, MD  
415-885-3792  
Thierry.jahan@ucsf.edu  
Box 1705  
UCSF HDFCCC  
San Francisco, CA 94158

DSMC Monitors  
Box 0128  
UCSF HDFCCC  
San Francisco, CA  
94143

## Appendix L. Risk Assessment for Institutional Studies:

The table below lists the risk assessment for the institutional studies monitored by the DSMC:

<b>Risk assignment</b>	<b>Study type</b>	<b>Monitoring</b>	<b>Surveillance</b>
<b>High</b>	Institutional Phase I therapeutic	Monitor all study patients in real-time as enrolled/ monitor through DLT period	Real time monitoring of AEs and SAE's weekly at site committees; DSMC monitors SAE every six weeks at DSMC Meetings
<b>High</b>	All Institutional therapeutic using gene therapy or vaccines, regardless of phase	Monitor all patients as enrolled/ monitor first three treatments/cycles	Real time monitoring of AEs and SAEs weekly at site committees; DSMC monitors SAE every six weeks at DSMC Meetings
<b>Moderate</b>	Institutional Phase II therapeutic	Audit all data in 20% of study patients twice per year	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors SAE every six weeks at DSMC Meetings
<b>Moderate</b>	Institutional Phase III therapeutic	Audit all data in 20% of study patients enrolled in trial twice per year	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors SAE every six weeks at DSMC Meetings
<b>Low</b>	Non-therapeutic trials	Audit all data in 20% of study patients enrolled in trial once per/year	DSMC monitors for SAEs every six weeks at DSMC Meetings