

# UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Plan (DSMP)



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## Data and Safety Monitoring Plan

### UCSF Helen Diller Family Comprehensive Cancer Center

#### I. Definitions

- **Auditing:** a quality assurance function where study conduct is reviewed on a less frequent basis (i.e., yearly review of a subset of charts after the participants are enrolled in the trial).
- **Conflict of Interest (COI):** this refers to situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting or reporting research.
- **Corrective and Preventative Action (CAPA):** the systematic investigation of the root causes of identified problems or risks in an attempt to prevent their recurrence (for corrective action) or to prevent occurrence (for preventive action).
- **Data and Safety Monitoring Board (DSMB):** specifically required for multicenter or consortium clinical trials with interventions that entail risk(s) to participants at multiple domestic and international sites.
- **Dose Limiting Toxicity (DLT):** Toxic effects that are presumably related to the drugs that are considered unacceptable (because of their severity and/or irreversibility) and that limit further dose escalation.
- **Maximum Tolerated Dose (MTD):** The highest dose of a drug or treatment in a dosing cohort which does not cause unacceptable side effects as per protocol.
- **Monitoring:** a quality control function where study conduct is routinely assessed on an on-going basis at every step of the trial (i.e., real-time review of all charts as participants are enrolled in the trial).

## **II. Introduction**

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

The University of California, San Francisco (UCSF) 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 Basic Sciences/Translational Sciences, Clinical Sciences, Population Sciences, Shared Resources, Education, Community Engagement, Immunotherapy, Cancer Research at Zuckerberg San Francisco General, Developmental Therapeutics, Program Development, Cancer Research at San Francisco Veterans Administration Medical Center, and Administration.

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

For the 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 health 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, etc.) and/or improve coping and quality of life 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 being evaluated in a manner that somehow affects medical decision-making for the participants beyond decision-making for standard of care treatment. 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, non-therapeutic trials with procedures that don't involve risk to the participants and 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 participants. Additionally, observational, and epidemiological studies and those that do not test interventions, are minimal risk trials and, thus, are not covered by this DSMP.

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

Clinical Research activities at the UCSF HDFCCC are supported by four units: (1) Protocol Review and Monitoring System (PRMS), Clinical Research Support Office (CRSO), Clinical Research Network Office (CRNO), and the Data and Safety Monitoring Committee (DSMC). All four units are guided by the Cancer Center Clinical Research Oversight Committee (CCCROC). Additionally, there are 16 Site Committees in the HDFCCC which are supported by these four units (Appendix A). The CRSO, PRMS, and the DSMC are each led by an experienced senior faculty member and an operations staff director. The faculty members of these units report to the HDFCCC Deputy Director. The Deputy Director reports to the HDFCCC President and Director.

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

The CCCROC provides oversight to the Clinical Protocol and Data Management (CPDM), the Protocol Review and Monitoring System (PRMS), and the Clinical Research Network Office (CRNO) (Appendix A). The CCCROC is comprised of clinical research leadership and clinical investigators from across the Cancer Center, including leadership from the Office of Community Engagement, IRB, CPDM, and PRMS, and is chaired by the Deputy Director of the Cancer Center, and reports directly to the Cancer Center Director. The PRMS includes the Protocol Review and Monitoring Committee (PRMC), and the disease specific and modality specific Site Committees. 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.

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

The goal of the PRMS 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 and Monitoring Committee (PRMC). The scope of the PRMC 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 PRMC is also charged with overall prioritization of all trials across the center. As described below, Site Committee review and approval is required before PRMC review of a trial. Although input and review from Site Committees is a critical component of the PRMC process, the PRMC has final authority regarding review, approval, monitoring and closure of trials. The PRMC meets on a monthly basis (Appendix A).

**Clinical Research Support Office (CRSO)**

The CRSO is composed of a Regulatory Affairs Unit and a Research Personnel Unit. 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 PRMS provides the scientific review and protocol feasibility, and the DSMC provides the monitoring and auditing oversight for the trials conducted by the CRSO (Appendix A).

**Clinical Research Network Office (CRNO)**

The goal of the Clinical Research Network Office (CRNO) is to develop Regional Affiliate Clinical Research Partnerships around the San Francisco Bay Area in order to develop, streamline, and improve oncology clinical research opportunities at these partner sites and to manage the UCSF National Clinical Trial Network (NCTN) and all associated affiliate sites. The CRNO team includes a Medical Director, Administrative Director, and an Operational Manager (Appendix A).

**Site Committees (SC)**

Each element of the clinical trials infrastructure (CRSO, CRNO, 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 (SC). There are 16 SC; ten are disease specific, and six are modality specific (Appendix C). All CCSG Programs have designated Site Committees. In addition to protocol review, prioritization, accrual, and scientific relevance monitoring, SC are responsible for the development, activation, and conduct of clinical trials. SC meet on at least a monthly basis with those committees reviewing phase I, or high-risk trials being required to meet at least on a weekly basis.

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

The DSMC is responsible for monitoring and auditing of all cancer-related interventional investigator-initiated trials in which UCSF is the Coordinating Site and the UCSF PI is the overall PI for the trial. The PRMC determines the level of risk for review of the trial, which in turn, determines the monitoring/auditing frequency as outlined in Appendix N. Monitoring is performed in real time as participants are enrolled in the trial and involves the review of all participants; whereas auditing occurs at designated time points (i.e., yearly) and is the review of a determined percentage of the enrolled participants in the trial.

The HDFCCC Director appoints the DSMC Chair. The DSMC Chair and the DSMC Director, together with the Deputy Director appoints other members of the DSMC. The DSMC members may serve in the committee indefinitely, as there is not a term limit. DSMC members are listed in Appendix D. The DSMC meets every six weeks throughout the calendar year.

Activities of the DSMC are overseen by the CCCROC. The DSMC Chair and Director provide regular progress report presentations to the CCCROC. In addition, the DSMC Director provides written reports to the HDFCCC Director and the HDFCCC CCCROC Chair detailing data and safety monitoring activities. Additionally, the minutes of each DSMC meeting are provided for review to the CCCROC Chair. When the DSMC identifies areas of concern, in addition to conferring with the CCCROC Chair, the DSMC Director notifies the PRMS, CRSO, and the UCSF IRB as warranted. The DSMC Director oversees the Monitor/Auditor Supervisor, the Education and Training Manager, and all Senior DSMC Monitors, Auditors (indirectly through the Monitor/Auditor Supervisor) in the DSMC. Of note, the DSMC Monitor and Auditor position functions are similar; however, the DSMC Monitor is focused on the real-time monitoring of the Phase I high-risk trials, whereas the DSMC Auditor is focused on the biannual or annual review of moderate and low-risk trials. Both positions report directly to the DSMC Monitor/Auditor Supervisor, who reports to the DSMC Administrative Director (Appendix B).

### **Phase I Trials**

Phase I dose escalation trials are monitored prior to the requested dose escalation of the dosing cohort. All participants, including participants enrolled at all participating sites for multicenter and consortium trials, are monitored through the Dose Limiting Cohort until the Maximum Tolerated Dose (MTD) is determined. Once the MTD is determined, then the trial is audited on an annual basis with twenty percent of the participants enrolled in this expansion cohort through their first five cycles of treatment, or until discontinuation, whichever is determined to be earlier. Scheduled auditing of participant source documents is complete after all files have been reviewed for five cycles of treatment. In addition, the records of 20% of enrolled participants are audited for the duration of trial accrual.

For Phase I high risk therapeutic trials that are not dose finding, all participants are monitored on a quarterly basis, assuming there have been accruals during that quarter, through the first cycle of therapy. Regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), as well as audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.



### **Vaccine/Gene Therapy Trials**

Vaccine/gene therapy trials are monitored on a quarterly basis, regardless of phase of the trial (assuming there have been accruals during that quarter ) through the first cycle of treatment. Monitoring of all enrolled participants in these trials will be complete after all enrolled participants have been monitored through the first cycle of treatment. Regulatory reviews of the trial, safety reviews (i.e., SAE reviews (including any findings of late or unexpected risks) and PV reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

### **Phase II and III Trials**

Phase II and III therapeutic trials are audited on an annual basis, with all data from 20% of the enrolled participants (up to a maximum of 10 participants per trial), including enrolled participants at each participating site for multicenter and consortium trials, audited by the DSMC Monitor/Auditor through their first five cycles of treatment (or discontinuation, whichever is earlier). If the Phase II/III trial has a safety lead-in cohort, then the DSMC will provide monitoring of all participants in this cohort prior to submission of a safety lead-in report to the DSMC Chair or Co-Chair for approval. After the safety lead-in request is granted by the DSMC Chair, the trial is audited on an annual basis with twenty percent of the participants reviewed through the first five cycles of treatment. The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this type of trial. Regulatory reviews of the trial, safety reviews (i.e., SAE reviews and PV reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

### **Dose Escalations/Safety Lead-In Reviews**

For dose escalation and safety lead-in requests, the DSMC Chair reviews the PI's submitted request and DSMC monitoring report. For Conflict of Interest concerns (i.e., the DSMC Chair is the PI or a Sub-Investigator on the trial being reviewed) or DSMC Chair absence/unavailability (e.g., vacation or otherwise out of office), then one of the DSMC Vice Chairs will review and approve these specific requests. Written authorization to proceed or a request for more information is issued within two business days of the request. The DSMC monitoring report and the escalation/safety lead-in request are then reviewed at the subsequent DSMC meeting. In the event that the committee does not concur with the DSMC Chair's approval, accrual is held while further investigation takes place.

### **International Trials**

As per the Policy on Minimum Standards for Partnerships with International Clinical Research Organizations, the overall PI must always utilize and contract with an international Clinical Research Organization (CRO) for the monitoring and auditing of non-US sub-sites. CCCROC and the DSMC must approve the choice of the CRO and their monitoring SOPs. The CRO must provide the

monitoring or auditing report for the DSMC's review. In general, the DSMC will not be providing monitoring/auditing services for International trials conducted in the HDFCCC; however, with DSMC Director and Chair or designee approval, the DSMC may provide audit function for low-risk international trials led by UCSF Investigators on a case-by-case basis with approval in advance of study activation.

### **Non-Therapeutic Trials**

For "greater than minimal risk" non-therapeutic trials, the assigned DSMC Monitor/Auditor will audit three of the enrolled participants once per year, with a maximum of ten participant charts audited during the entire course of reviewing this trial until IRB closure. If blood or tissue banking trials are determined to be "greater than minimal risk", then only SAEs recorded in OnCore will be reviewed at each DSMC meeting for these trials. Auditing of patient data for the trial will be complete after 10 enrolled participants have been audited. Regulatory reviews of the trial, safety reviews (i.e., SAE reviews and PV reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

### **Regulatory Audits**

An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, Delegation of Authority (DOA) logs, FDA Form 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennial basis by the DSMC for regulatory compliance (Appendix G).

### **Subject Monitoring Visit Reports (MVRs)**

DSMC MVRs are sent to the PI and study team for follow-up review and action items and are formally reviewed at the DSMC meeting following the monitoring/auditing visit(s). The study team will be provided a Monitoring Visit Report (MVR) within 20 business days after last day of the monitoring visit. The MVR contains action items for the study team to review and provide response. The responses to these follow-up action items will be due to the DSMC monitor/auditor from the PI, and the study team within 20 business days unless otherwise specified (e.g., for urgent time-consuming changes) (Appendix F).

### **Serious Noncompliance Issues**

If there are serious or continuing compliance issues or an increased risk to participant safety in a study trial or study program, the DSMC may mandate a temporary enrollment suspension for a trial, an Investigator's research portfolio, or a study program until a robust corrective and preventative action plan (CAPA) is developed by the PI and study team or program. The DSMC will notify the CRSO Medical Director and the CRSO Director of the suspension so they may help develop, implement, and ensure compliance with the CAPA. The PI and the study

team will notify the IRB of record, the Industry Sponsor (i.e., Pharmaceutical Sponsor), and the NCI Program Director for NCI-CTEP trials (as applicable) of this suspension on trial activities. Once the suspension has been lifted by the DSMC, then the PI and the study team will 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. (Appendices J and K).

#### **Protocol Violation/Consent Incident Reviews**

All Protocol Violations and Consent Incidents that occur in any cancer trial are reviewed by the DSMC (and the CRSO for CRSO-specific trials) to ensure that a proper root cause analysis has been completed and that there is an adequate and feasible corrective and preventative action (CAPA). After the study teams have submitted the Protocol Violation/Consent Incident Report to the IRB, the IRB will then determine if the report will need to be reviewed by the full IRB Panel. If so, the IRB QIU Director will send the report to the DSMC Director (or designee) for review to provide determination if the event merits a Serious Noncompliance or Serious and Continuing Noncompliance determination and to provide any additional information that would be helpful to the IRB Panel to make their final decision with regards to this determination. The DSMC Director (or designee) will also notify the Principal Investigator (PI) of this review. The DSMC Director or designee will send the completed DSMC Protocol Violation/Consent Incident Review Form to the IRB Quality Improvement Unit (QIU) Director (Appendix L).

### **IV. Data and Safety Monitoring Plan Templates:**

#### **Required Elements**

All clinical trials conducted at the UCSF HDFCCC, except for minimal risk trials, must have a satisfactory DSMP template consistent with this HDFCCC DSMP, which is described in detail in the protocol. These plans will be reviewed by both the DSMC and the PRMC as part of the protocol approval process and are evaluated in relation to the potential risks and scale of the trial (Appendix M).

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

The PI will conduct review of data and patient safety at Site Committee meetings. Phase I trials will undergo weekly review; Phase II and III trials will undergo at least 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.
- Significant toxicities as described in the protocol.
- Dose modifications per protocol.
- Interim analysis review (as available and required).

## VI Implementation of Reporting Requirements

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

- The DSMC reviews all grade(s) 1 - 5 adverse events (AEs), regardless of causality and relationship, for Phase I trials and all grade 3-5 AEs, regardless of causality and relationship, for Phase II and III trials, including non-therapeutic trials, when monitoring or auditing the trials. The DSMC may also review grade 1 and 2 AEs for Phase II and III trials if applicable per protocol (i.e., events of special interests). These AEs are tracked in OnCore as per the table below.
- The DSMC reviews all SAE Reports, for all clinical trials (i.e., Industry-Sponsored, Investigator-Initiated, and National Group) via an OnCore Report at the DSMC Meetings. All deaths related to the Investigational Product, Investigational Device, or trial procedures must be reported by the PI to the DSMC Chair or designee within one business day of study team awareness.
- SAEs, regardless of the relationship to the study, will be tracked in OnCore, the UCSF HDFCCC Clinical Trial Management System (CTMS) as per the table below:

Study Phase	Investigator Initiated	National Group/Cooperative Group	Industry
1	Clinically significant grade 1-5 AEs, regardless of causality and relationship	SAEs	SAEs
2	Grade 3-5 AEs, regardless of causality and relationship	SAEs	SAEs
3	Grade 3-5 AEs, regardless of causality and relationship	SAEs	SAEs
Non-Therapeutic	Grade 3-5 AEs related to study procedures	SAEs	SAEs

- The overall PI is responsible for the notification of other participating institutions of all unexpected SAEs (new risks) if the clinical trial involves multiple institutions and UCSF is the lead institution according to the protocol.

### B. Study Progress

- The DSMC will review DSMC monitoring reports and protocol stopping rules to determine whether a trial 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 or designee will

provide communication to the IRB of any decisions for enrollment suspension within a study program for study non-compliance issues.

## **VII. Monitoring Procedure**

The DSMC Monitor/Auditor manages the logistics associated with the monitoring review sessions. Once the clinical trial is identified for review, the DSMC Monitor/Auditor arranges for a selection of cases to monitor from among the subjects registered in OnCore based upon the guidelines in Appendix H. The PI and CRCs are notified via e-mail in advance of a scheduled monitoring session (i.e., at the time of the completion of the previous monitoring visit) 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 and Consortium trials, the participating sites are responsible for providing the electronic source documents for review.

The DSMC Monitor/Auditor reviews the regulatory files on a biennial basis and uses OnCore and iRIS to review the following in the trials reviewed:

- IRB approval dates for protocols and amendments
- IRB approved informed consent forms.
- IRB approved study documents (e.g., patient diaries).
- SAEs and PV Reports to the IRB (as applicable).
- Approved Protocol Eligibility Exceptions
- IND Safety Reports.

Additionally, the DSMC reviews the following at the scheduled monitoring or auditing visit:

- The medical records as the source documents and verifies data entry in the electronic case report forms (OnCore or comparable eCRF).
  - The source documents are reviewed to ensure that there is adherence to the protocol, accurate data entry, 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 and documented.
- Any required screening tests and procedures are obtained as per protocol.
- All eligibility criteria reviewed to ensure that the study participant 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 SAEs.

- Review of possible dose limiting toxicities (DLTs).
- Adherence to patient follow-up requirements.

Following the completion of the monitoring session, the DSMC Monitor/Auditor will complete the Monitoring Visit Report (MVR) (see Appendix F, G, H, and I), which describes the findings of this monitoring visit. The study is given an overall evaluation by the DSMC Monitor/Auditor, review and approved by the DSMC Monitor/Auditor Supervisor, DSMC Director, and the DSMC Chair or designee. The overall finding of the MVR is deemed with one of the following evaluations:

- **Acceptable with no follow-up action items.**
- **Acceptable with follow-up items.**
- **Significant findings with follow-up response to the DSMC required.** Significant findings include multiple protocol violations leading to a serious noncompliance determination. The follow-up response and CAPA are due to the DSMC Director within 10 business days.
- **Unsatisfactory findings with a halt in enrollment and a corrective and preventative action plan required within 10 business days to the DSMC Director.** Unsatisfactory findings include multiple safety and data integrity findings, including multiple major serious non-compliance report determinations which increases the probability of an external regulatory inspection and requires a hold on enrollment to ensure that additional training, revised workflows, etc. can be implemented to address further significant safety and data integrity issues. The DSMC Chair or designee will notify the IRB regarding the results of this audit/monitoring visit.

## **VIII. Data Quality Control**

### **A. Pre-Industry Sponsored Audit and Pre-Regulatory Agency Inspection**

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 participant review, and pharmacy review. The DSMC Auditor/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 AEs including grading and attribution of each event
- Reporting of 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 CAPA.

## **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 J).

The DSMC Director and the DSMC Chair or designee will communicate this formal decision to the PI and study team, as well as to HDFCCC Leadership and the IRB. 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 lift the enrollment suspension (Appendix K). 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 PRMS, as well as to the PI and study team. Additionally, the PI will notify the NCI Program Director if this is an NCI-CTEP trial or the Industry-Sponsor will be notified if this is an Industry-Sponsored trial (i.e., Pharmaceutical trial) of this removal of accrual suspension. Once the study program accrual is resumed, the DSMC Director and the DSMC Chair or designee will meet with the PI and study team on a regular basis to review accrual, staffing, and issues encountered with the trials within the study program. These meetings will continue 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, PRMS, the PI and the study team will be notified, as well as the NCI Program Director if this is an NCI-CTEP trial and the Industry-Sponsor if this is an Industry-Sponsored (i.e., Pharmaceutical trial).

## **IX. Conflict of Interest**

The voting members of the DSMC must recuse themselves from discussion during the DSMC meeting for any review (including MVRs) of their trials in which they are the PI, or if the DSMC members (or relevant family members) have any financial interests in the trial being discussed).

The DSMC Chair cannot sign a MVR or review and approve a dose escalation report or safety lead-in report from a trial monitored/audited in their SC. Instead, the DSMC Chair must have one of the DSMC Vice Chairs sign the monitoring report, as well as review and approve the dose escalation or safety lead-in reports.

## **X. Guidelines for Establishing and Operating a UCSF HDFCCC Data and Safety Monitoring Board (DSMB)**

### **1. Membership**

- a. The HDFCCC DSMC Auditors/Monitors will perform auditing and 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. Yearly DSMB reports for all Multicenter and Consortium trials will be reviewed at the DSMC Meetings.
  - ii. DSMB meetings occur as part of the regularly scheduled DSMC meetings (i.e., every 6 weeks)
- b. Elements for Review
  - i. A written summary of status, toxicity and outcomes of the clinical trial will be prepared by the study team. The summary will be submitted to the DSMC Director no later than 24 hours from the next scheduled DSMB meeting for review and approval by the DSMC Chair or Vice Chair prior to review by the DSMB committee members.



- ii. The DSMC Director or designee will develop the formal DSMB report for the DSMC Chair or Vice Chair's signature and the report will be reviewed at the next DSMC meeting.
- iii. The DSMB report may contain recommendations concerning whether to close the trial, report the results, or continue accrual or follow-up by the DSMB committee members.

### **3. Recommendations**

- a. It is the responsibility of the PI and the 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 provided to the PI. 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 DSMB must be informed of the reason for disagreement.
- e. The DSMB Chair (or Vice 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. 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.

## **XII. Education and Training Office**

The DSMC Education and Training Office (ETO) is an integral part of the DSMC. The office is charged with on-boarding, training and ongoing education with regards to clinical research in the UCSF HDFCCC of all clinical research staff, including Investigators, clinical research coordinators and nurses, program project managers (PPMs), and Regulatory team members at all campuses of UCSF, including the network sites in the San Francisco Bay Area.

Investigators: All HDFCCC Investigators are required to complete an Investigator training program on the proper conduct of clinical research (Appendix E). New investigators are required to complete their training prior to being added as an Investigator (i.e., listed on the FDA 1572 form) on any study in the HDFCCC, and this training must be completed prior to PRMC approval of a trial where they are listed as the PI. Site Committees are responsible for notifying the DSMC wherever training is required. Investigators are required to complete refresher training via e-Learning modules on an every three years basis frequency.

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

CRCs conducting cancer clinical research trials. The module courses are taught in-person and include the following topics:

- Introductory Courses:
  - Intro to Clinical Research
  - Intro to Oncology
  - Research Job Overview
  - Intro to IRB/Regulatory
  - Intro to DSMC
  - Intro to Investigator Initiated Trials
  - CRC Overview of Adult Infusion Center
- Core Courses:
  - Protocol Training
  - Informed Consent
  - Study Coordination Part 1 – Screening
  - Study Coordination Part 2 – Eligibility
  - Adverse Event and Serious Adverse Event
  - Notification of New Risk & Re-consent
  - Protocol Deviations and Violations
  - Data & Monitoring Visit
  - Patient Travel Reimbursement
  - Billing and Finance

A final quiz is administered once all core courses have been completed.

A separate training series is offered to staff on the study teams who have regulatory responsibilities on the study teams (primarily PPMs and Supervisors responsible for study activation and maintenance):

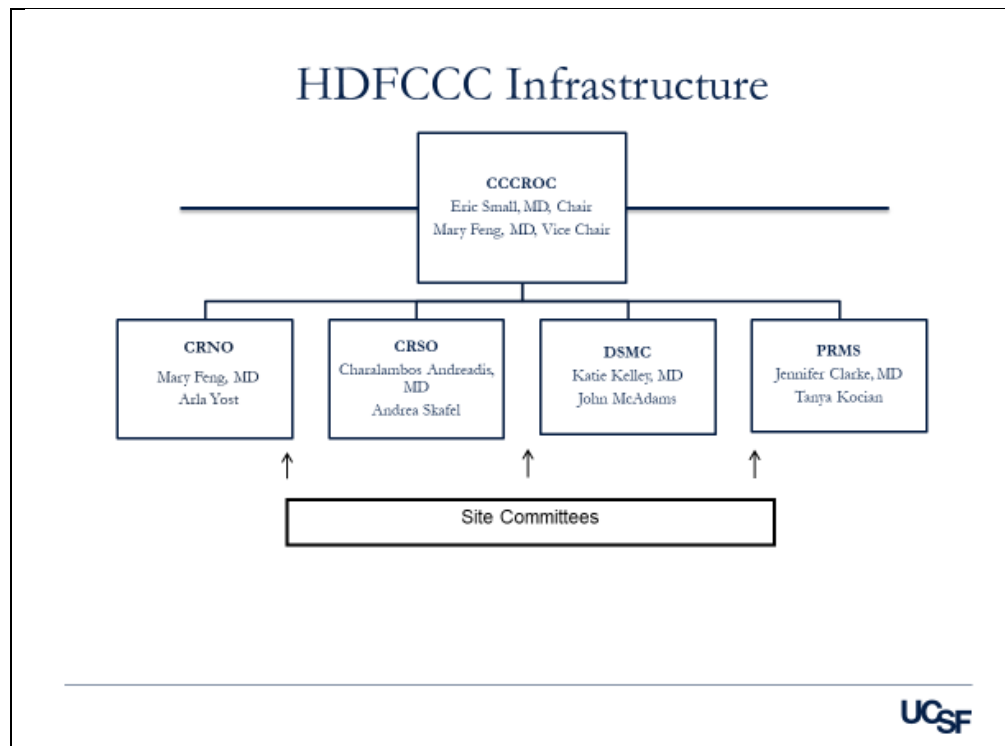
- Site Committee
- PRMC Submission and Approval
- Industry Sponsored Start-up
- Amendments
- Regulatory Binder
- Expanded Access
- Investigator Initiated Study Start-up
- PPM Introduction to Regulatory

The Continual Education Series are offered in order to expand the skill set of the clinical research staff:

- Consenting for Non-therapeutic Trials (for CRCs, RNs, other research staff who will obtain informed consent for non-therapeutic trials)
- Consenting Non-English-Speaking Participants
- Communication and Health Literacy (for staff who are patient-facing)
- Compliance (for staff using the e-Regulatory platform)

**Appendix A: HDFCCC Clinical Trials Infrastructure:**

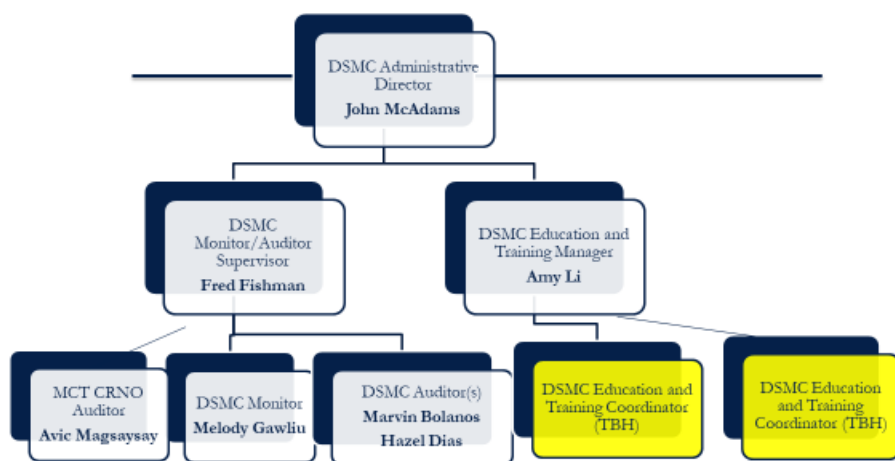
*CCCROC coordinates the activities of the four units, each of which have a Faculty Director/Chair and an Administrative Director.*



## **Appendix B: DSMC Organization:**

*The two units of the DSMC (Monitoring/Auditing and Education and Training) and their staff managers and personnel.*

### DSMC Organization Chart



## **Appendix C. UCSF HDFCCC Site Committees and Chairs**

### **Site Committee**

Breast Oncology  
Cancer Immunotherapy Program (CIP)  
Cancer and Tobacco Control (CTC)  
Cutaneous Oncology  
Experimental Therapeutics Department  
Gastrointestinal Oncology  
Genitourinary Oncology  
Gynecologic Oncology  
Hematopoietic Oncology (Adult)  
Molecular Imaging and Radionuclide Therapy  
Neurologic Oncology  
Oral, Head & Neck Oncology  
Pediatric Oncology  
Radiation Oncology  
Survivorship and Symptom Science  
Thoracic Oncology

### **Chair**

John Park, MD  
Peter Sayre, MD  
Tung Nguyen, MD  
Katy Tsai, MD  
Pamela Munster, MD  
Emily Bergsland, MD  
Rahul Aggarwal, MD  
Edwin Alvarez, MD  
Thomas Martin, MD  
Thomas Hope, MD  
Nicholas Butowski, MD  
Alain Algazi, MD  
Anu Banerjee, MD  
Mary Feng, MD  
TBD  
Collin Blakely, MD

## **Appendix D. UCSF HDFCCC Data and Safety Monitoring Committee (DSMC)**

### **Data and Safety Monitoring Committee Voting Members**

Katie Kelley, MD	Chair and Gastrointestinal Oncology	Professor
Michelle Melisko, MD	Vice Chair and Breast Oncology	Associate Professor
Jennie Taylor, MD	Vice Chair and Neurologic Oncology	Associate Professor
Kristin Shimano, MD	Pediatric Oncology	Associate Professor
Weiyun Ai, MD	Hematologic Oncology	Associate Professor
Vadim Koshkin, MD	Genitourinary Oncology	Assistant Professor
Collin Blakely, MD	Thoracic Oncology	Assistant Professor
Steve Braunstein, MD	Radiation Oncology	Associate Professor
Edwin Alvarez, MD	Gynecologic Oncology	Associate Professor
Tom Hope, MD	MIRT*	Assistant Professor
Joan Hilton, PhD	Biostatistics Core	Professor
Laura Quintal, PharmD	Investigational Drug Service	Assistant Professor

\*Molecular Imaging and Radionuclide Therapy

### **Data and Safety Monitoring and Office & Education and Training Office Non-Voting Members**

John F. McAdams, MS, CCRP	DSM Director
Fred Fishman, BS, CCRP	DSM Auditor/Monitor Supervisor
Amy Li, MPA, CCRP	DSM Education and Training Manager
Marvin Bolanos, BS, CCRP	DSM Senior Auditor
Hazel Dias, BS, CCRP	DSM Senior Auditor
Avic Magsaysay, MD, CCRP	DSM CRNO Senior Auditor
Melody Gawliu, BA, CCRP	DSM Senior Monitor



## Appendix E: PI Training Checklist

### UCSF INVESTIGATOR TRAINING CHECKLIST

Investigator Name: \_\_\_\_\_

#### Investigator Training Requirements

Training Topic	Completion Date	Investigator Initial	ETM/DSMC Director Initials
Introduction to UCSF HDFCCC			
Cancer Center Clinical Research Oversight Committee (CCCROC)			
Site Committee <ul style="list-style-type: none"><li>Site Committee Membership</li></ul>			
Protocol Review and Monitoring System/ Protocol Review Committee <ul style="list-style-type: none"><li>PRC Review Levels</li></ul>			
Data and Safety Monitoring Committee <ul style="list-style-type: none"><li>DSMC Charter</li></ul>			
Department research staff & roles <ul style="list-style-type: none"><li>Protocol Development Team</li><li>Coverage Analyst &amp; Budget</li><li>Research 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)<ul style="list-style-type: none"><li>Regulatory paperwork</li><li>Trainings</li><li>Trial/order templates</li></ul></li><li>Sign off on final budget, calendar, and MCA</li><li>IIT/IST</li><li>MCT IIT</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></ul></li></ul>			

## UCSF INVESTIGATOR TRAINING CHECKLIST

Training Topic	Completion Date	Investigator Initial	ETM/DSMC Director Initials
<ul style="list-style-type: none"> <li>▪ Consenting non-English speaking subjects</li> <li>▪ Telephone consent</li> <li>○ Screening window</li> <li>○ Eligibility criteria</li> <li>○ Enrollment</li> </ul>			
<b>PI responsibilities for clinical trials</b> <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>			
<b>PI responsibilities for clinical trials</b> <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>			
<b>PI responsibilities for clinical trials</b> <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>			
<b>Emergency Use, Compassionate Use/Expanded Access</b>			
<b>Audit vs. Inspection</b> <ul style="list-style-type: none"> <li>• How to prepare</li> <li>• Roles &amp; responsibilities</li> </ul>			

## UCSF INVESTIGATOR TRAINING CHECKLIST

Training Topic	Completion Date	Investigator Initial	ETM/DSMC Director Initials
<ul style="list-style-type: none"> <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 Investigator onboarding training requirements.

Investigator Signature & Date	Education & Training Manager Signature & Date	DSMC Director Signature & Date

## Appendix F. Data and Safety Monitoring Reports: Subject Monitoring Report

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

Study Title:			
CCs:			
UCSF IRB Approval # IRB Expiration Date:		Site No:	
Principal Investigator:		Study Coordinator:	
Study status:	Total accrual to date	Total number of subjects reviewed	Type of visit
Auditor/Monitor:			
Date(s) of Monitoring Visit:			

Areas of Review	Assessments
<b>I. Study Management</b>	
a) The consent process was implemented per UCSF IRB's 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 in OnCore or other eDC system (if applicable)	
g) Phase I trials only: Current Cohort: _____ DLTs were identified in this cohort.	
h) Phase I trials only: PI will submit a formal Dose Escalation Report Form to the DSMC for review and approval after completion of this monitoring visit.	
i) Phase II trials with Safety Lead-In: PI will submit a formal Safety Lead-In Report Form to the DSMC for review and approval after completion of this monitoring visit.	
<b>II. Toxicity documentation and management</b>	
j) Subjects were dosed correctly.	
k) Dose modifications per protocol.	
Comments regarding study management:	

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AutoSave Off Times New Roman DSMC Subject Monitoring Report (version 05Nov2019) - Saved Table Tools John McAdams MJ Share Comments

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

Subject Review	
Subject initials:	Subject ID #:
Visits Dates Monitored:	Subject's Current Status:
Areas of Review	Assessments
<b>I. Informed Consent</b>	
a) Subject consented with correct ICF version with all required signatures by key study personnel listed in IRIS.	Choose an item.
b) New risks communicated with subjects as per HDFCCC Safety Reporting Policy.	Choose an item.
<b>II. Eligibility</b>	
c) All screening and pretreatment procedures completed correctly.	Choose an item.
d) Subject eligibility confirmed with supporting documentation and signed off by the PI, CRM, and CRC.	Choose an item.
<b>III. Treatment</b>	
e) Treatment per protocol confirmed.	Choose an item.
<b>IV. Assessment</b>	
f) All assessments completed per protocol.	Choose an item.
g) Disease response assessment completed per protocol.	Choose an item.
<b>V. Adverse Event (AE) and Serious Adverse Event (SAE)</b>	
h) AEs and SAEs were confirmed by source documents.	Choose an item.
i) SAE Report was provided to the Sponsor, UCSF IRB, and/or FDA (if applicable) within the allowed period for SAE reporting as per protocol.	Choose an item.
<b>VI. Review of Reports / Submissions / Note to Files (NTF)</b>	
j) All Protocol Violations (PV) or Consent Incidents (CI) were reported to the UCSF IRB or IRB of record with a CAPA reviewed by the DSMC.	Choose an item.
k) If a PV or CI was deemed as a Serious Noncompliance finding by the UCSF IRB or other IRB of record, then the DSMC was notified and an appropriate CAPA response was developed by the PI.	Choose an item.
<b>VII. Data Management</b>	
l) Subject was entered with treatment status up to date in OnCore.	Choose an item.
m) Study data was entered with open queries in OnCore.	Choose an item.
n) GCP was followed throughout the chart (i.e., all errors are lined out and initialed/dated).	Choose an item.

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

o) Chart is organized chronologically and properly tagged for visits, labs, etc. Choose an item.

Comments regarding subject review:

Overall Summary Evaluation of Visit:

☐ Acceptable with no follow-up action items

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

☐ Significant findings: with follow-up CAPA response to the DSMC due within 10 business days. The HDFCCC DSMC Chair or DSMC designee will notify the IRB and PRC regarding the results of this audit/monitoring visit.

☐ Unsatisfactory findings with halting of enrollment of new subjects and a CAPA response to the DSMC due within 10 business days. The HDFCCC DSMC Chair or DSMC designee will notify the IRB and PRC regarding the results of this audit/monitoring visit

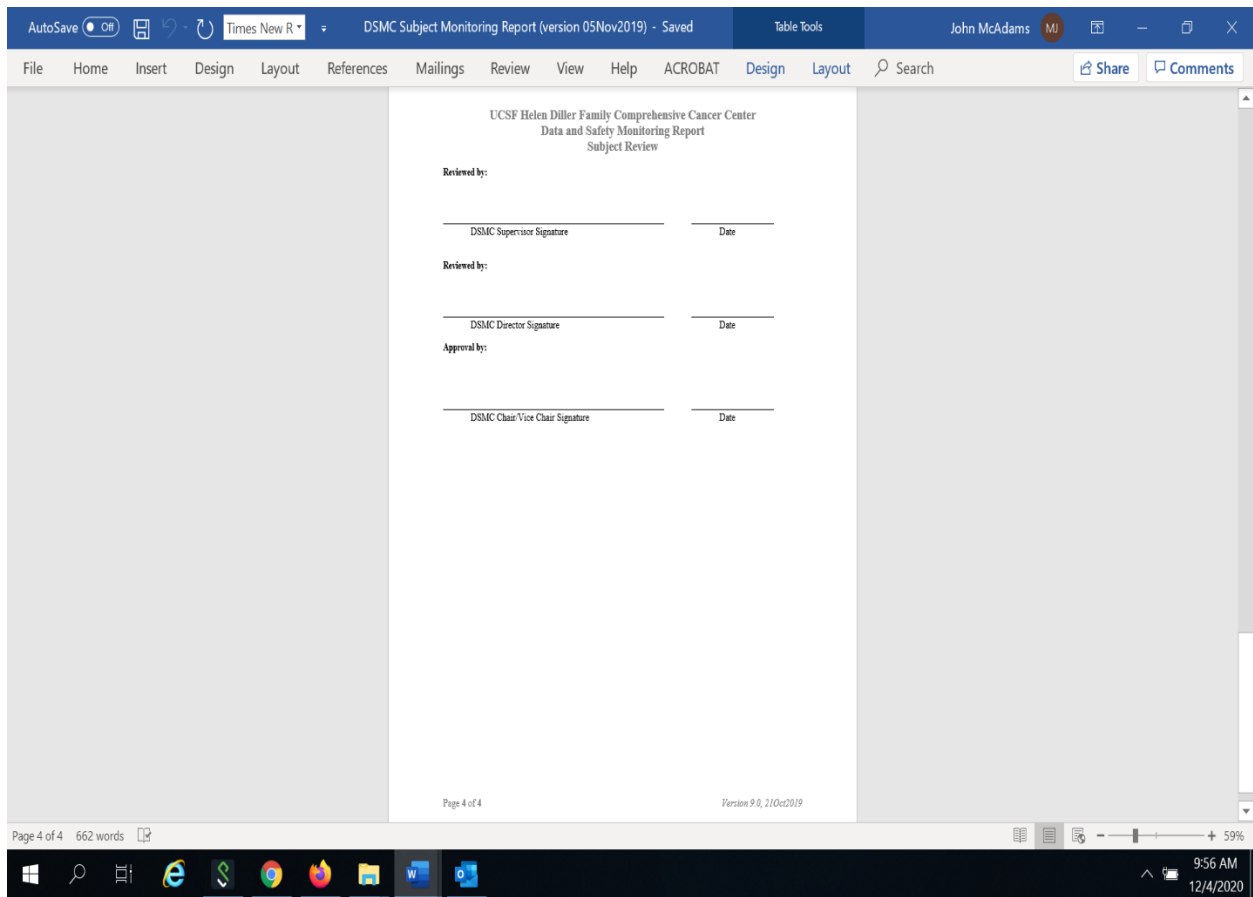
Audited/Monitored by:

Monitor's/Auditor's Signature Date

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

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

Study Title:	
CC#:	
Auditor Monitor:	
Date(s) of Monitoring Visit:	
Study Status:	
UCSF IRB Approval # IRB Expiration Date:	Site No:
Principal Investigator:	Study Coordinator:

Areas of Review	Assessments
<b>I. Protocol</b>	
a) Documentation of the current IRIS approved protocol in IRIS, zip drive, or Completion?	Choose an item.
b) Have all protocol signature pages been signed and dated by the PI?	Choose an item.
c) Are all prior UCSF IRB approved protocol versions in IRIS, zip drive, or Completion?	Choose an item.
<b>II. Consent</b>	
d) Are all versions of the ICF filed in IRIS, zip drive, or Completion?	Choose an item.
<b>III. Investigator Brochure</b>	
a) Is the current IB filed in IRIS, zip drive, or Completion?	Choose an item.
b) Are all prior IB approved versions filed in IRIS, zip drive, or Completion?	Choose an item.
c) If study drug is FDA approved, is the package insert on file in OoCore, zip drive or in Completion?	Choose an item.
d) Is there IRIS documentation of submission(s) of IBs on file with acknowledgement approval?	Choose an item.
e) Timely UCSF IRB submission of IBs as per IRB Policy?	Choose an item.
<b>IV. IND/IDE Application and FDA Approval</b>	
f) Is the initial application on file in OoCore, zip drive, or in Completion?	Choose an item.
g) Was the FDA Confirmation Letter of IND Status submitted to UCSF IRB (for IND-held ITT's)?	Choose an item.
h) Was the first patient enrolled in the trial 30 days or more after receiving FDA confirmation letter?	Choose an item.

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

i) If PI holds the IND for ITTs, have the IND Annual Reports been filed as required with the FDA? (If exempt, not applicable).	Choose an item.
<b>V. PRC Approvals</b>	
j) Did the PRC approvals precede the UCSF IRB approvals?	Choose an item.
k) PRC approved Protocol Versions are documented in OnCore?	Choose an item.
l) PRC amendment with Protocol and SOC is documented in OnCore under detail section?	Choose an item.
<b>VI. UCSF IRB Approvals</b>	
m) Any lapses in UCSF IRB approval? If yes, where any patients enrolled during this time?	Choose an item.
n) IRIS approvals on file in IRIS, zip drive, or Complan for initial submission?	Choose an item.
o) If PI holds the IND for ITTs, were the FDA confirmations letters submitted to the UCSF IRB and is the IND number on the front of the cover page?	Choose an item.
p) If multicenter trial, are participating site's IRB approvals on file in OnCore, zip drive, or Complan?	Choose an item.
q) Are the key study personnel who can consent on file in IRIS under application for the coordinating site?	Choose an item.
<b>VII. Other Approvals</b>	
r) Documentation of Biosafety Committee (vaccines) approval?	Choose an item.
s) Documentation of Radiation Safety approval?	Choose an item.
<b>VIII. Serious Adverse Event Section</b>	
t) SAE reports submitted to the UCSF IRB with supporting documentation?	Choose an item.
u) SAE reports submitted to the Sponsor with supporting documentation?	Choose an item.
v) If a Multicenter trial, did the coordinating site communicate new risks from the SAEs to the participating site(s) in the teleconference minutes?	Choose an item.
w) If a Multicenter trial, are the participating site(s) submitting SAEs to the coordinating site for submission to the FDA as per protocol?	Choose an item.
x) For IND-held ITTs, were MedWatch forms submitted to the FDA as per timeline in the protocol?	Choose an item.
<b>IX. Protocol Violations or Incident Reports</b>	
y) PVs reported to UCSF IRB per guidelines and timelines with supporting documentation?	Choose an item.
<b>X. Study Personnel Documents</b>	
z) Is there staff training documentation (i.e., CITI training, protocol and amendment training, etc.)? Is there documentation of training for the original	Choose an item.

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

protocol and all amendments for all staff on the Delegation of Authority (DOA) Log?	
aa) Completed and signed Delegation of Authority (DOA) Log? Were all study responsibilities delegated from the PI to the study team as per their credentials and expertise?	Choose an item.
bb) Signed Curriculum Vitae (CV) for all Investigators?	Choose an item.
cc) MD/ND Licenses on file for all Investigators?	Choose an item.
dd) Completion of both the FDA Form(s) 1571 and FDA 1572 (for IND held ITIs) or FDA Form(s) 1572 (for non-IND held ITIs or Industry Sponsored Trials (ISTIs))?	Choose an item.
ee) Was the FDA Form 1572 updated for changes in staff or labs, scans, etc. as applicable?	Choose an item.
XI. Screening and Enrollment Log	
ff) Is there documentation of a Screening and Enrollment Log?	Choose an item.
XII. Laboratory Documentation	
gg) Are the CLIA certifications, CAPs, lab license, laboratory normal reference ranges, and the CV of the Lab Director filed in the regulatory files?	Choose an item.
XIII. Other Documents	
hh) Are there Site Committee Meeting Minutes on file for this trial?	Choose an item.
ii) Was all correspondence to and from the Sponsor, other sites (for multicenter trials), etc. filed in regulatory files?	Choose an item.
Comments regarding regulatory review:	
Overall Summary Evaluation of Visit:	

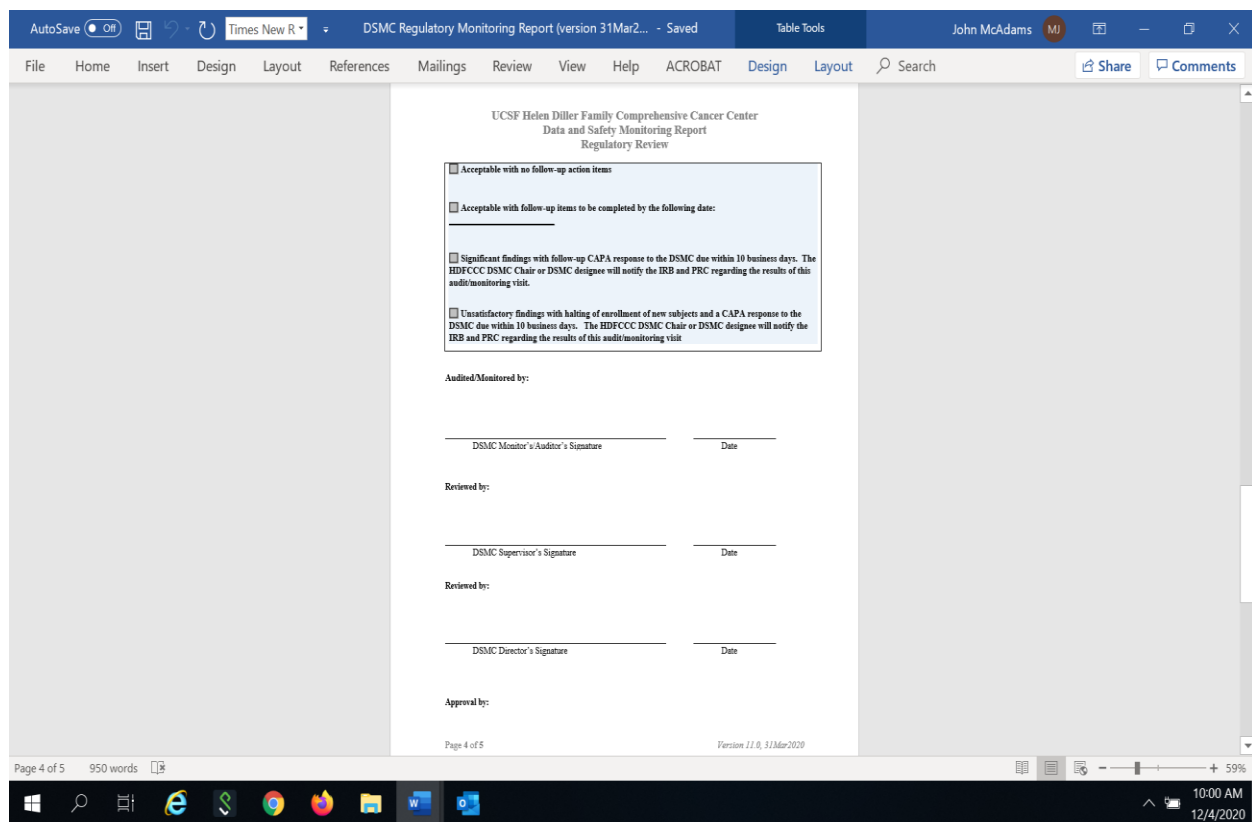
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Revision #5 (16Sep2021)



## Appendix H: Subject or Regulatory Monitoring Follow-up Report

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UCSF Helen Diller Family Comprehensive Cancer Center  
Data and Safety Subject or Regulatory Monitoring Report  
Action Items Worksheet

**Follow-up Action Items to be completed by Study Team by MMDDYYYY:**

Action Item: (to be completed by DSMC Monitor/Auditor)	Comment: (to be completed by study team)	Completed (Yes/No & Date) (to be completed by study team)	Acceptable Response to Action Items (Yes/No) (to be completed by DSMC Monitor/ Auditor)

Study Team Representative Signature\* \_\_\_\_\_ Date \_\_\_\_\_

DSMC Monitor/Auditor Signature\*\* \_\_\_\_\_ Date \_\_\_\_\_

\*To be signed off once all action items are completed by the Study Team Representative.  
\*\*To be signed off by the DSMC Monitor/Auditor at the next monitoring visit.

Data and Safety Subject or Regulatory Monitoring Report Action Items Worksheet  
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## Appendix I: DSMC CRNO Chart Review Checklist for UCSF and Affiliates

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Data Safety Monitoring Report  
Chart Review Checklist for UCSF and Affiliates

Study Title:	
Study #:	Study Phase:
Protocol version:	Site No:
Sponsor:	Study Status:
Principal Investigator:	Study Coordinator:
Subject ID:	Subject status:
Chart Review Completed by:	Date:

I. Informed Consent	Assessment
a. Bill of Rights <sup>(1)</sup> HIPAA <sup>(2)</sup> (if applicable) and ICF <sup>(3)</sup> were obtained properly as per Sponsor, IRB on record and regulatory guidelines. Consenting documents were completed prior to any procedures occurring for the trial. Consenting process was documented in the patient's chart. <ul style="list-style-type: none"><li>Subject and Investigator signed on the same date</li><li>Investigator is listed on DTL (if applicable)</li><li>For re-consents, Subject and Investigator signed on the same date and that there was a clear discussion of the process (or consent documentation form) in the subject's chart.</li></ul>	Choose an item
II. Eligibility	
b. Eligibility Criteria was completed and signed by the Investigator <ul style="list-style-type: none"><li>PI signed and dated eligibility checklist.</li><li>EC document matched the EC in the protocol version.</li><li>Source document were on file to support each inclusion/exclusion criteria</li><li>Investigator signed/dated all sources docs (Source docs included Study ID/MRN and Study ID # and Name)</li></ul>	Choose an item
III. Assessment	
c. Medical History/Baseline Conditions were completed and signed by the investigator.	Choose an item
d. MD dictations for medical history items, adverse events, and concomitant medications were available for review.	Choose an item
e. All labs, scans, etc. were reviewed and signed by investigator: <ul style="list-style-type: none"><li>Investigator indicated abnormal values as Clinically Significant (CS) or Non-Clinically Significant (NCS).</li><li>CS events are access for grade per CTCAE, attribution and expectedness</li><li>CS events are documented as AE in AE log</li></ul>	Choose an item
f. Restaging scans were completed per protocol specifications, if completed outside window: follow up with PI to determine if this is Protocol Deviation vs Protocol Violation.	Choose an item
g. All investigator's orders were completed.	Choose an item
IV. Treatment	

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Data Safety Monitoring Report

Chart Review Checklist for UCSF and Affiliates

h. Treatment per protocol confirmed.	Choose an item.
<b>V. Adverse Events (AE) and Serious Adverse Event (SAE)</b>	
i. Adverse Event (Toxicity Sheets) and Concomitant Medications forms were completed and signed by the investigator. All SAEs were submitted to the Sponsor, IRB on record, FDA, etc. (as applicable) per timelines in the protocol and as per regulations.	Choose an item.
<b>IV. Data Management</b>	
j. Single Patient Exemptions, Protocol Violations, Notes to File, etc. (if applicable) were available on patient files.	Choose an item.
k. ECR was followed throughout chart (i.e., cross-outs are initialed and dated).	Choose an item.
l. Subject chart was organized chronologically and properly tagged for visits, labs, RCF, etc.	Choose an item.
m. Off Study Treatment form was completed and signed dated by PI (if applicable)	Choose an item.

Comments regarding subject review:

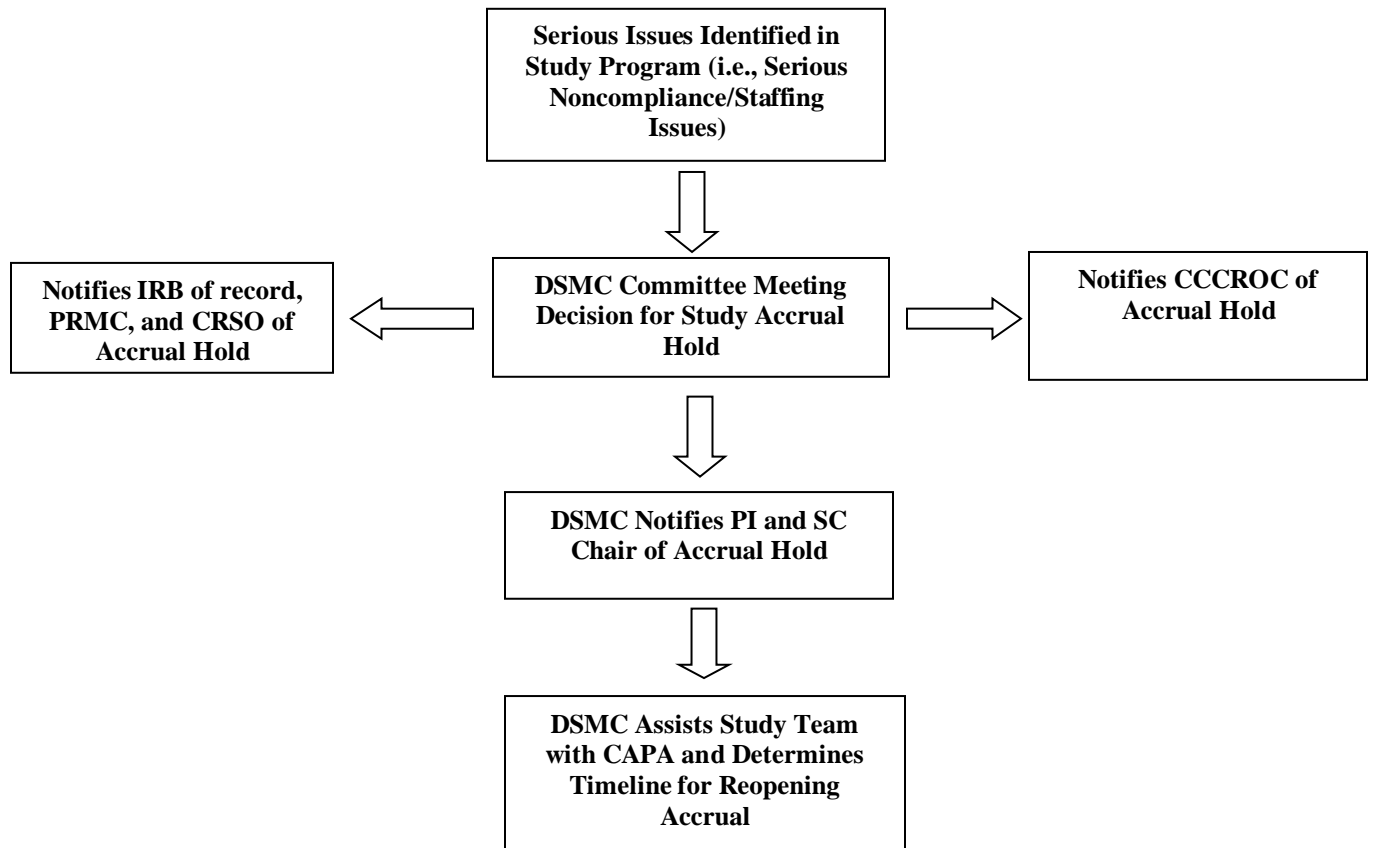
Follow-up items to be completed by Study Group:

Action Item: (to be completed by auditor)	Comment: (to be completed by study group)	Completed (Yes/No & Date) (to be completed by study group)	Acceptable Response to Action Items (Yes/No) (to be completed by auditor)

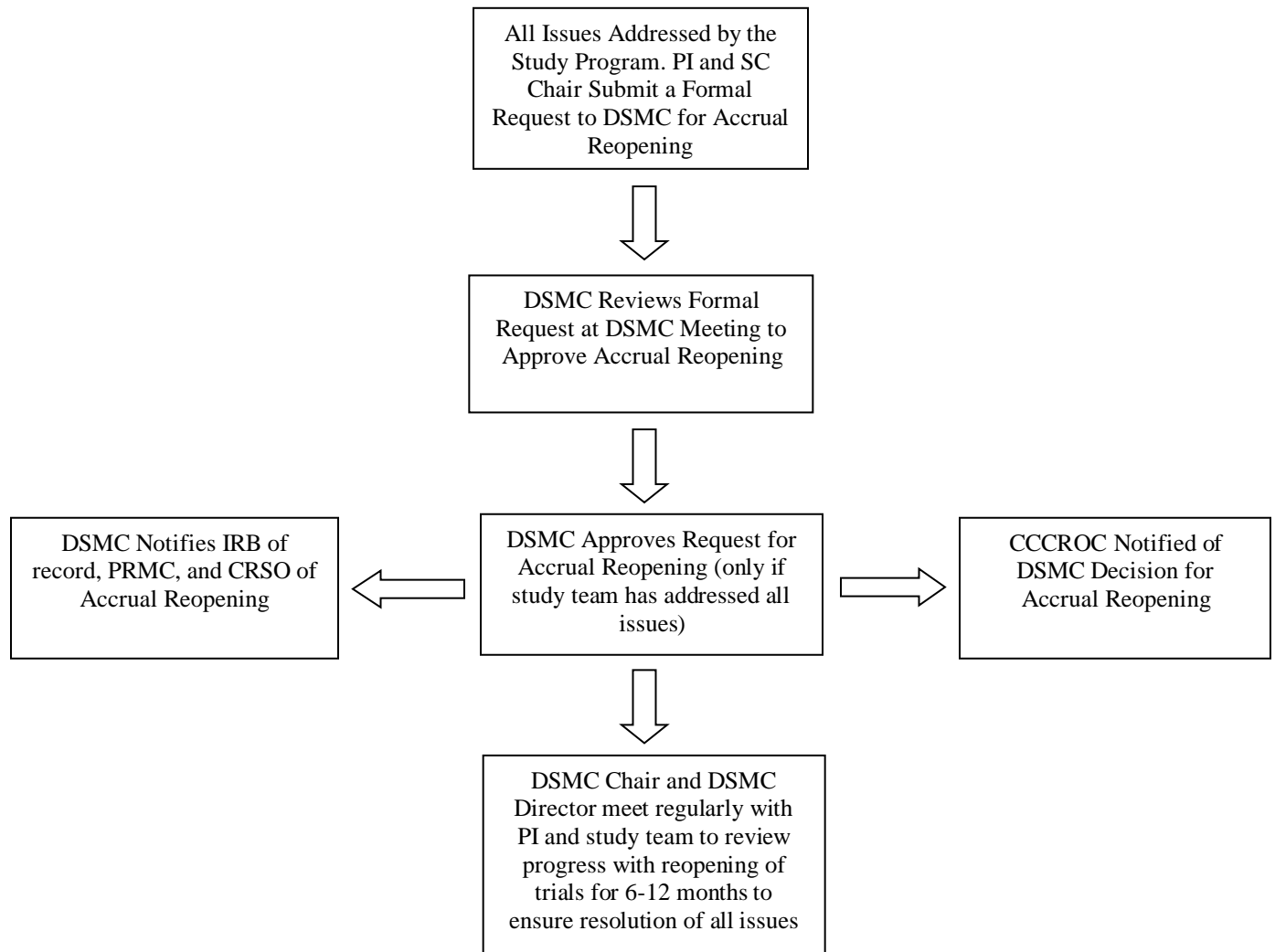
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**Appendix J: DSMC Remediation Process: Mandatory Study Program Accrual Hold (Not including Voluntary Accrual Holds)**



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





## Appendix L: DSMC Protocol Violation/Consent Incident Review Form

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UCSF Helen Diller Family Comprehensive Cancer Center

**DSMC Protocol Violation(PV)/Consent Incident (CI) Review Form**

Date: \_\_\_\_\_

The UCSF DSMC Chair (or Vice Chair if there is conflict of interest as per the NCI approved Data and Safety Plan (DSP)) and the DSMC Administrative Director have reviewed the following Protocol Violation (PV) or Consent Incident (CI) Report from the UCSF IRB as the PV/CI report meets the criteria for full Committee review by an IRB analyst or Chair: \_\_\_\_\_

CCIR/IR: \_\_\_\_\_

Date of IRB Committee Meeting scheduled to review PV/CI: \_\_\_\_\_

IRB Committee Panel to review PV/CI: \_\_\_\_\_

Date PI notified of this review by the DSMC: \_\_\_\_\_

Based upon review of the PV report and the proposed Corrective and Preventative Action (CAPA) plan, the DSMC Committee makes the following recommendation:

☐ PV/CI does not meet criteria for SNC or CSNC; proposed CAPA provides satisfactory mitigation of PV/CI

☐ Warrants full committee review of PV/CI event(s) and of the proposed CAPA to determine compliance status by IRB.

Comments: \_\_\_\_\_

\_\_\_\_\_  
DSMC Administrative Director/Designee's Signature Date

\_\_\_\_\_  
DSMC Chair/Vice Chair's Signature Date

HDfCCC DSMC PV/CI IRB Form (v. 04Dec2020)

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## **Appendix M. DSMP Templates for Investigators to Insert into IIT Protocols**

**Note to Investigators:** These plans are templates for protocol preparation.

## **Appendix M.1 (Single Site) Phase I Dose Escalation**

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

#### **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 participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Participant monitoring prior to dose escalations
- Review of participant data in each cohort
- Review of serious adverse events
- Approval of dose escalation by DSMC Chair or Vice Chair
- Minimum of biennial regulatory auditing

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

Investigators will conduct a continuous review of data and participant safety at weekly site committee meetings. The discussions are documented in the site committee meeting minutes.

All institutional phase I therapeutic dose escalation trials are designated with a high-risk assessment. The data for all enrolled participants in each dosing cohort is monitored by a DSMC Monitor/Auditor prior to approval of the dosing cohort, and includes a review of all study information through the Dose Limiting Toxicity (DLT) visit of the trial up until the maximum tolerated dose (MTD) is determined. Once the MTD is determined, the trial will then be audited annually, with 20 percent of the enrolled study participants audited for the first five cycles of treatment. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Once the MTD is determined, then the trial is audited on an annual basis with twenty percent of the participants enrolled in this expansion cohort that are audited through their first five cycles of treatment.

Scheduled auditing of participant source documents is complete after all files have been reviewed for five cycles of treatment (20% of participants). Monitoring of enrolled participants in the dose expansion phase of the trial will be complete after 20% of enrolled participants have been monitored through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews

and Protocol Violation (PV) reviews), as well as audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

### **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 investigational agent(s) or study procedure, 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 investigational agent(s) or study procedure. Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** – clearly not related to the investigational agent(s) or study 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 attribution assignment.

#### **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 adverse experience\*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

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

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). 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 Vice Chair) and DSMC Director within one business day.

### **3.3 Dose Escalations**

At the time of dose escalation, the PI submits a written and signed Dose Escalation Report to the DSMC Chair (or Vice Chair) and DSMC Director 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 Committee meeting. In the event that the committee does not concur with the DSMC Chair's (or Vice 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 PI will notify the DSMC via report 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 PI voluntarily holds enrollment in the trial due to safety issues, the DSMC Chair (or Vice Chair) and DSMC Director must be notified within one business day via e-mail, and the IRB must be notified as per IRB reporting regulations.

**Data and Safety Monitoring Committee Contacts:**

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San Francisco, CA 94158

## **Appendix M.2 (Single Site): High-Risk Vaccine or Gene-Therapy**

### **Data and Safety Monitoring Plan for a High-Risk Vaccine or Gene-Therapy Institutional Trial (Single Site)**

#### **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 participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Participant monitoring on a quarterly basis (depending on study accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

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

Investigators will conduct a continuous review of data and participant safety at weekly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional vaccine or gene therapy therapeutic trials, regardless of the study phase, are designated with a high-risk assessment. The data is monitored by a DSMC Monitor/Auditor on a quarterly basis (depending on accrual) as participants are enrolled in the trial through the first month of study drug therapy. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Monitoring of all enrolled participants in these trials will be complete after 10 participants have been reviewed. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

#### **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 investigational agent(s) or study procedure, 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 investigational agent(s) or study procedure. Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** – clearly not related to the investigational agent(s) or study 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 attribution assignment.

### 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 adverse experience\*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.



Serious adverse event reporting will be in accordance with the all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:  
<https://irb.ucsf.edu/adverse-event>

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). 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) and DSMC Director within one business day.

### **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 via report 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 (or Vice Chair) and the DSMC Director must be notified within one business day via e-mail and the IRB must be notified as per their reporting regulations.

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

Katie Kelley, MD (DSMC Chair)  
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[Katie.kelley@ucsf.edu](mailto:Katie.kelley@ucsf.edu)  
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San Francisco, CA 94158

## **Appendix M.3 (Single Site): Phase II or III Institutional Trial**

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

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

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

- Annual auditing (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

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

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II and III therapeutic trials are audited on an annual basis, with all data from 20% percent of the enrolled participants audited by the DSMC Monitor/Auditor.

The assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

#### **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 investigational agent(s) or study procedure, 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 investigational agent or study procedure. Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** – clearly not related to the investigational agent(s) or study 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 attribution assignment.

### 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 adverse experience\*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:  
<https://irb.ucsf.edu/adverse-event>

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). 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) and DSMC Director within one business day.

### **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 via report 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 voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting regulations.

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

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## **Appendix M.4 (Single Site): Phase II Trial with Safety Lead-In Phase**

### **Data and Safety Monitoring Plan: Institutional (Single Site) Phase II Trial with Safety Lead-In Phase**

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

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

- Review of all participant data in safety lead-in phase
- Approval to enroll past safety lead-in phase by DSMC Chair or Vice Chair
- Annual auditing after safety lead-in phase
- Review of serious adverse events
- Minimum of biennial regulatory auditing

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

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the results of each participant's treatment are discussed and documented in the site committee minutes.

All institutional Phase II trials with a safety lead-in are designated with a high-risk assessment during the safety lead-in phase and a moderate risk assessment for the remainder of the trial. During the safety lead-in phase, the DSMC will audit all visits through the first cycle of treatment for all participants enrolled in this phase of the trial.

After the completion of enrollment in the safety lead-in phase, the Principal Investigator will submit a report to the DSMC Chair outlining all AEs, SAEs, and DLTs (as defined in the protocol) with a request to proceed onto the next phase of the study. Within two business days of receipt, the DSMC Chair or designee will review the report and issue written authorization to proceed or a request for more information. The report is then reviewed at the subsequent DSMC meeting.

After DSMC authorization to enroll beyond the safety lead-in phase is granted, study data is audited annually, with a random selection of 20% of the participants reviewed (or at least three participants if the calculated value is less than three). Additionally, the assigned DSMC Monitor/Auditor will review no more than a total of 10 participant charts through five cycles of treatment during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items

from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

### **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 investigational agent(s) or study procedure, 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 the investigational agent(s) or study procedure.

Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** – clearly not related to the investigational agent(s) or study procedure.

All Grade 3-5 adverse events entered into OnCore will be reviewed on a monthly basis at the UCSF Coordinating Center's Site Committee. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution assignment.

#### **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 adverse experience\*,



- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

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

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, All SAEs are reviewed and monitored by the DSMC 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 an SAE involves death, and 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, then the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

### **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 is responsible for notifying the DSMC via report 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 Principal Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and DSMC Director must be notified within one business day.

**Data and Safety Monitoring Committee Contacts:**

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## **Appendix M.5 (Single Site): Interventional Non-therapeutic Institutional Trial**

### **Data and Safety Monitoring Plan for a Non-therapeutic Institutional Trial**

#### **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 participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Annual auditing
- Review of serious adverse events
- Minimum of biennial regulatory auditing

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for participant safety for all HDFCCC institutional clinical trials. Greater than minimal risk nontherapeutic studies are characterized as low risk studies due to the trial design, as there isn't administration of drugs or complementary therapy that puts the participants at significant risk.

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

Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the status of each participant is discussed and documented in the site committee minutes.

For “greater than minimal risk” nontherapeutic trials, the assigned DSMC Senior Monitor/Auditor will audit three of the enrolled participants once per year, with a maximum of ten participant charts audited during the entire course of auditing this trial until IRB closure.

If blood or tissue banking trials are determined to be “greater than minimal risk”, then only Serious Adverse Events (SAEs) recorded in OnCore will be reviewed at each DSMC meeting for these trials.

After completion of each auditing visit, the DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 10 enrolled participants have been audited. However, regulatory reviews of the trial, safety reviews

(i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

### 3. Review and Oversight Requirements

#### 3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered expected or unexpected and whether or not considered associated with the study intervention or procedure, 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 study intervention or procedure. Attribution categories are:

- **Definite** – clearly related to the study intervention or procedure.
- **Probable** – likely related to study intervention or procedure.
- **Possible** – may be related to study intervention or procedure.
- **Unrelated** – clearly not related to the study intervention or 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 adverse experience\*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:  
<https://irb.ucsf.edu/adverse-event>

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. 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 and is determined to be possibly, probably, or definitely related either to the study intervention or procedure, the Investigator or his/her designee must notify the DSMC Chair or Vice Chair and DSMC Director within one business day.

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

If at any time the Investigator voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified as per IRB reporting requirements.

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

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San Francisco, CA 94143

## **Appendix M.6 (Multicenter) Interventional Non-Therapeutic Multicenter Institutional Trial**

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

#### **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 participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Annual auditing of participant data
- Review of serious adverse events
- Minimum of annual DSMB reports
- Minimum of biennial regulatory auditing

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for participant safety for all domestic sites for HDFCCC Multicenter and Consortium institutional clinical trials. The International sites must be audited by a Clinical Research Organization (CRO) that is formally approved by the HDFCCC Cancer Center Clinical Research Oncology Committee (CCCROC) and the HDFCCC DSMC via the [HDFCCC Policy of Minimum Standards for Partnership with International CROs](#).

For “greater than minimal risk” nontherapeutic trials, the assigned DSMC Senior Monitor/Auditor will audit three of the enrolled participants once per year, with a maximum of ten participant charts (across all sites) during the course of reviewing this trial until IRB closure. If blood or tissue banking trials are determined to be “greater than minimal risk”, then only Serious Adverse Events (SAEs) recorded in OnCore will be reviewed at each DSMC meeting for these trials.

Auditing of all enrolled participants in these trials will be complete after 10 enrolled participants have been audited. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

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. Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings

where the status of each participant is discussed and documented in the site committee 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. The data (i.e., copies of source documents) from the participating sites will be downloaded into the CRA console of OnCore prior to the monitoring visits or the DSMC will be provided with access to the participating site's electronic medical record (EMR) system, in order for the DSMC to perform a remote audit of the participating site's compliance with the protocol.

## **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 intervention or procedure 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 the study intervention or procedure. Attribution categories are:

- **Definite**— clearly related to the study intervention or procedure.
- **Probable**—likely related to the study intervention or procedure.
- **Possible**— may be related to the study intervention or procedure.
- **Unrelated**— clearly not related to the study intervention or 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 assignment for adverse events that occurred at 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 adverse experience\*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:  
<https://irb.ucsf.edu/adverse-event>

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). All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within one 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 of the submission of the SAE report to all required reporting agencies will be documented in OnCore.

If a death occurs during the treatment phase of the study 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 one business day from the participating site(s) and the Study Chair must then notify the DSMC Chair (or Vice Chair) and the DSMC Director within one business day of this notification.

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

If at any time the Study Chair voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and DSMC Director must be notified within one business day and the IRB must be notified as per their reporting requirements.

### **3.4 Data and Safety Monitoring Board (DSMB) Reports**

Data and Safety Monitoring Board (DSMB) Reports which provide information on trial accrual, participant safety, and data integrity will be provided to all sites, including the domestic and international sites, on an annual basis. The DSMB Report will be signed by the DSMC Chair (or Vice Chair) and provided to the DSMC Committee for formal review at the next scheduled DSMC Committee meeting.

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

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415-353-9888  
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## **Appendix M.7 (Multicenter): Phase 1 Dose Escalation**

### **Data and Safety Monitoring Plan for a Multicenter Institutional Trial (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 participant safety for all HDFCCC institutional clinical trials and cancer-specific trials at UCSF. A summary of DSMC activities for this trial includes:

- Participant monitoring prior to dose escalation.
- Review of participant data in each cohort
- Approval of dose escalation by DSMC Chair or Vice Chair
- Review of serious adverse events
- Minimum of biennial regulatory auditing

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

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 trial and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and participant safety at weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for participant safety for all domestic sites for HDFCCC Multicenter and Consortium institutional clinical trials. The International sites must be monitored by a Clinical Research Organization (CRO) that is formally approved by the HDFCCC Cancer Center Clinical Research Oncology Committee (CCCROC) and the HDFCCC DSMC via the [HDFCCC Policy of Minimum Standards for Partnership with International CROs.](#)

All multicenter phase I dose escalation trials are monitored prior to the requested dose escalation of the dosing cohort. All participants are monitored through the Dose Limiting Cohort until the Maximum Tolerated Dose (MTD) is determined. Once the MTD is determined, then the trial is audited on an annual basis with twenty percent of the participants enrolled in this expansion cohort that are audited through their first five cycles of treatment. Scheduled auditing of participant source documents is complete after all files have been reviewed for five cycles of treatment (20% of participants). For Phase I high risk therapeutic trials that are not dose finding, all participants are monitored on a quarterly basis (depending on accrual) through the first cycle of therapy.

DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Monitoring of enrolled participants in the dose expansion portion of the trial will be complete after 20% of enrolled participants have been monitored through two cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), as well as audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

### **Multicenter communication**

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. 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 participant scheduled to be enrolled at a site. Dose level assignments for any participant scheduled to begin treatment must be confirmed by the UCSF Coordinating Center via e-mail.

If a participant experiences a Dose Limiting Toxicity (DLT), the UCSF Coordinating Center will notify all sites within one business day of awareness. If the DLT occurs at a participating site, the local investigator must report the DLT to the UCSF Coordinating Center within one business day. The Study Chair has one business day (after first becoming aware of the event at either the UCSF Coordinating Center or the participating site) in which to report the DLT information to all 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. 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 or the DSMC will be provided with access to the participating site's electronic medical record (EMR) access in order for the DSMC to perform remote monitoring of the participating site's compliance with the protocol and applicable FDA regulations

### **Dose Escalations**

At the time of dose escalation, a written and signed Dose Escalation Report will be submitted to the DSMC Chair (or Vice Chair) and DSMC Director 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 Committee meeting. In the event that the committee does not concur with the DSMC Chair's (or Vice Chair's) decision, study accrual is held while further investigation takes place.

## **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 investigational agent or study procedure. Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** – clearly not related to the investigational agent(s) or study procedure.

All adverse events entered into OnCore will be reviewed on a weekly basis at the UCSF Coordinating Center's Site Committee meetings. The UCSF Site Committee will review

and discuss the selected toxicity, grade, and the attribution assignment for the adverse events that occurred at both 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 adverse experience\*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:  
<https://irb.ucsf.edu/adverse-event>

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). 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 Vice Chair) and the DSMC Director within one business day of this notification.

### **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 via a report. 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 voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day via e-mail and the IRB must be notified their reporting requirements.

### **3.4 Data and Safety Monitoring Board (DSMB) Reports**

Data and Safety Monitoring Board (DSMB) Reports which provide information on trial accrual, participant safety, and data integrity will be provided to all sites, including the domestic and international sites, on an annual basis. The DSMB Report will be signed by the DSMC Chair (or Vice Chair) and provided to the DSMC Committee for formal review at the next scheduled DSMC Committee meeting.

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



Katie Kelley, MD (DSMC Chair)  
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San Francisco, CA 94158

## **Appendix M.8 (Multicenter) High Risk Vaccine or Gene Therapy**

### **Data Safety Monitoring Plan for High Risk Vaccine or Gene Therapy Multicenter Trial**

#### **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 participant safety for all HDFCCC institutional clinical trials. A summary of DSMC activities for this trial includes:

- Participant monitoring on a quarterly basis (depending on trial accrual)
- Review of serious adverse events
- Minimum of biennial regulatory auditing

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

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 trial and for monitoring its safety and progress at all participating sites. The Study Chair will conduct a review of data and participant safety at the weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for participant safety for all domestic sites for HDFCCC Multicenter and Consortium institutional clinical trials. The International sites must be monitored by a Clinical Research Organization (CRO) that is formally approved by the HDFCCC Cancer Center Clinical Research Oncology Committee (CCCROC) and the HDFCCC DSMC via the [HDFCCC Policy of Minimum Standards for Partnership with International CROs.](#)

All vaccine or gene therapy therapeutic trials, regardless of the study phase, are designated with a high-risk assessment. The data is monitored by a DSMC Monitor/Auditor on a quarterly basis as participants are enrolled in the trial through the first month of study drug therapy. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Monitoring of all enrolled participants in these trials will be complete after all enrolled participants have been monitored through first cycle of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

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.

### **Multicenter communication**

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. 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
- 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. The data (i.e., redacted copies of source documents) from the participating sites will be downloaded into the CRA module of OnCore® prior to the monitoring visits or the DSMC will be granted with access to the participating site's electronic medical record (EMR) in order for the monitoring of the participating site's compliance with the protocol and applicable FDA regulations

## **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 investigational agent or study procedure. Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.

- **Unrelated** – clearly not related to the investigational agent(s) or study procedure.

All adverse events entered into OnCore® will be reviewed on a weekly basis at the UCSF Coordinating Center's Site Committee meetings. The UCSF Site Committee will review and discuss the selected toxicity, grade, and the attribution assignment for the adverse events that occurred at both 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 adverse experience\*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

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

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. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within one 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 one business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or Vice Chair and DSMC Director within one business day of this notification.

### **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 holds enrollment or stops the study due to safety issues, the DSMC Chair or Vice Chair and DSMC Director must be notified within one business day via e-mail and the IRB must be notified within their reporting requirements.

### **3.4 Data and Safety Monitoring Board (DSMB) Reports**

Data and Safety Monitoring Board (DSMB) Reports which provide information on trial accrual, participant safety, and data integrity will be provided to all sites, including the domestic and international sites, on an annual basis. The DSMB Report will be signed by the DSMC Chair (or Vice Chair) and provided to the DSMC Committee for formal review at the next scheduled DSMC Committee meeting.

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

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## **Appendix M.9 (Multicenter) Phase II or III Trial**

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

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

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

- Annual auditing (depending on accrual).
- Review of serious adverse events.
- Minimum of a biennial regulatory auditing visit.

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

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 trial and for auditing its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and participant safety at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for participant safety for all domestic sites for HDFCCC Multicenter and Consortium institutional clinical trials. The International sites must be audited by a Clinical Research Organization (CRO) that is formally approved by the HDFCCC Cancer Center Clinical Research Oncology Committee (CCCROC) and the HDFCCC DSMC via the [HDFCCC Policy of Minimum Standards for Partnership with International CROs](#).

All institutional Phase II or III therapeutic trials are designated with a moderate risk assessment. The data is audited by a DSMC Monitor/Auditor on an annual basis with a random selection of 20% of the participants (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for review or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than 10 total participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

The participating site's source documents are audited remotely via either review of redacted source documents downloaded by the site into the CRA console of OnCore and/or via access to the site's electronic medical records. The DSMC Monitor/Auditor will audit no more than three participant charts at each participating site during the course of auditing this trial.

### **Multicenter communication**

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. 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.
- 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 data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the remote monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and applicable 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 the investigational agent(s) or study procedure. Attribution categories are:



- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** – clearly not related to the investigational agent(s) or study 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 grade 3-5 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 attribution assignment 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 adverse experience\*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:  
<https://irb.ucsf.edu/adverse-event>

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 one business days of becoming aware of the event. The SAEs are reviewed and audited 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 Vice Chair and the DSMC Director within 1 business day of this notification.

### **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 Chair (or Vice Chair) and the DSMC Director at the time the increased rate is identified via a report. 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 (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified within their reporting guidelines.

### **3.4 Data and Safety Monitoring Board (DSMB) Reports**

Data and Safety Monitoring Board (DSMB) Reports which provide information on trial accrual, participant safety, and data integrity will be provided to all sites, including the domestic and international sites, on an annual basis. The DSMB Report will be signed by the DSMC Chair (or Vice Chair) and provided to the DSMC Committee for formal review at the next scheduled DSMC Committee meeting.

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

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## **Appendix M.10 (Multicenter) Phase II or III Trial with Safety Lead-In Phase**

### **Data and Safety Monitoring Plan: Multicenter Phase 2 or 3 Trial with Safety Lead-In**

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

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

- Review of all participant data in safety lead-in phase.
- Approval to enroll past safety lead-in phase by DSMC Chair or Vice Chair.
- Annual auditing after safety lead-in phase (depending on accrual).
- Review of serious adverse events.
- Minimum of a biennial regulatory auditing visit.

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

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 trial and for auditing its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and participant safety at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for participant safety for all domestic sites for HDFCCC Multicenter and Consortium institutional clinical trials. The International sites must be audited by a Clinical Research Organization (CRO) that is formally approved by the HDFCCC Cancer Center Clinical Research Oncology Committee (CCCROC) and the HDFCCC DSMC via the [HDFCCC Policy of Minimum Standards for Partnership with International CROs](#).

All institutional Phase II or III therapeutic studies with a lead-in are designated with a high-risk assessment during the safety lead-in phase and a moderate risk assessment. During the safety lead-in phase, the DSMC will audit all visits through the first cycle of treatment for all participants enrolled in this phase of the trial.

After the completion of enrollment in the safety lead-in phase, the Study Chair will submit a report to the DSMC Chair outlining all AEs, SAEs, and DLTs (as defined in the protocol) with a request to proceed onto the next phase of the trial. Within two business days of receipt, the DSMC Chair or designee will review the report and issue written authorization to proceed or a request for more information. The report is then reviewed at the subsequent DSMC meeting.

After DSMC authorization to enroll beyond the safety lead-in phase is granted, study data is audited by a DSMC Monitor/Auditor on an annual basis with a random selection of 20% of the participants (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for review or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than 10 total participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

The participating site's source documents are audited remotely via either review of redacted source documents downloaded by the site into the CRA console of OnCore and/or via access to the site's electronic medical records. The DSMC Monitor/Auditor will audit no more than three participant charts at each participating site during the course of auditing this trial.

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

### **Multicenter communication**

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. 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 data (i.e., copies of source

documents) from the participating sites will be downloaded into the PC console of OnCore prior to the remote monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and applicable FDA regulations.

### **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 investigational agent(s) or study procedure, 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 the investigational agent(s) or study procedure. Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** – clearly not related to the investigational agent(s) or study 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 grade 3-5 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 assignment 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 adverse experience\*,
- Inpatient hospitalization or prolongation of existing hospitalization,

- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other 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 that changes the risk/benefit ratio of the study.

\* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

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

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 one business days of becoming aware of the event. The SAEs are reviewed and audited 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, then 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 Vice Chair) and the DSMC Director within 1 business day of this notification.

### **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 Chair (or Vice Chair) and the DSMC Director at the time the increased rate is identified via a report. 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 (or Vice Chair) and the DSMC Director must be notified within one business day and the IRB must be notified within their reporting guidelines.

### **3.4 Data and Safety Monitoring Board (DSMB) Reports**

Data and Safety Monitoring Board (DSMB) Reports which provide information on trial accrual, participant safety, and data integrity will be provided to all sites, including the domestic and international sites, on an annual basis. The DSMB Report will be signed by the DSMC Chair (or Vice Chair) and provided to the DSMC Committee for formal review at the next scheduled DSMC Committee meeting.

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## **Appendix N: 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 dose-escalation therapeutic	Monitor all participants in real-time as prior to dose escalation through DLT period. Once DLT is determined, then audit 20% of participants through first five cycles of therapy.	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 participants on a quarterly basis as enrolled through the first cycle of therapy.	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 first five cycles of treatment in 20% of study participants on an annual basis	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 II therapeutic with Safety Lead-In	Monitor all patients in the safety lead-in cohort, then audit first five cycles of treatment in 20% of study participant thereafter on an annual basis	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 first five cycles of treatment in 20% of participants on an annual basis	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 with study procedures that are above minimal risk	Audit three participants enrolled in trial once per year, with a maximum of ten total participants reviewed for any given trial.	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors for SAEs every six weeks at DSMC Meetings
<b>Minimal Risk</b>	Non-therapeutic trials with minimal risk procedures	Not responsible for auditing	Not responsible for auditing