UCSF Helen Diller Family Comprehensive Cancer Center

University of California at San Francisco Helen Diller Family Comprehensive Cancer Center Data and Safety Monitoring Plan (DSMP)



NCI Designated Comprehensive Cancer Center

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1 Definitions

- **Auditing**: A quality assurance function whereby 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).
- **Clinical Trial**: 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. 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.
- **Conflict of Interest (COI)**: A situation 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.
- **Data and Safety Monitoring Board (DSMB)**: Independent patient safety and data integrity committee specifically required for multicenter or consortium clinical trials with interventions that entail risk(s) to participants at multiple domestic and international sites.
- **Dose Escalation**: A dose finding process to determine the optimal dose(s) of a treatment regimen based upon safety (maximum tolerated dose (MTD)) and other parameters (e.g., efficacy, pharmacokinetics) for further study; may be used to define a Recommended Phase 2 Dose (RP2D).
- **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 in a dose-finding study.
- **Institutional Trial**: Studies in which the UCSF HDFCCC PI is the Sponsor of the trial and holds the Investigational New Drug (IND) application.
- **Maximum Tolerated Dose (MTD)**: The highest dose of a drug or treatment in a dosing cohort in a dose finding study which does not cause unacceptable side effects as per protocol.

- **Monitoring**: A quality control function through which 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 a trial).

2 Introduction

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, Developmental Therapeutics, Program Development, and Immunotherapy, and Administration, along with the HDFCCC Partner sites: Benioff Children's Hospital - Oakland (BCHO), Washington Hospital Healthcare System (WHHS), Cancer Center – Berkeley, Cancer Center – San Mateo, Cancer Research at Zuckerberg San Francisco General, and the Cancer Research at San Francisco Veterans Administration Medical Center.

3 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: 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 up to the HDFCCC Deputy Director. The Deputy Director reports to the HDFCCC President and Director.

3.1 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-and modality-specific Site Committees. The CPDM includes the Clinical Research Support Office (CRSO) and the Data and Safety Monitoring Committee (DSMC). The CRSO, CRNO, PRMS, and the DSMC are independent units whose activity is overseen and integrated by the CCCROC.

3.2 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).

3.3 Clinical Research Support Office (CRSO)

The CRSO includes a Regulatory Affairs Unit and a Research Personnel Unit. The Regulatory Affairs Unit is responsible for protocol development (institutional trials), safety reporting, federal compliance, informed consent form development, IRB applications and review, and regulatory training for study team staff, as well as coordination of activities with the UCSF Office of Research. The Research Personnel Unit consists of clinical research coordinators (CRCs), CRC leadership, protocol project managers (PPMs) described below, and staff associate directors. This unit is responsible for recruiting, hiring, onboarding, training, supervision, and performance management of all clinical research personnel. CRCs facilitate daily operations and execution of study protocols including source document collection, data entry, patient visit coordination and navigation, and monitoring visits. PPMs provide project management for every clinical trial in each site committee and are responsible for timely and compliant trial activation, maintenance, and closeout, as described below.

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).

3.4 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).

3.5 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 Cancer Center Support Grant (CCSG) Programs have designated Site Committees. In addition to protocol review, prioritization, accrual, and scientific relevance monitoring, SCs are responsible for the development, activation, and conduct of clinical trials. SCs 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.

3.6 Data and Safety Monitoring Committee (DSMC)

The DSMC is responsible for monitoring and auditing of all cancer-related interventional investigator-initiated trials (IITs) in which UCSF is the sponsor, 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 and auditing frequency as outlined in Appendix N. Monitoring is performed in real time as participants are enrolled in high-risk trials and involves the review of all participants; whereas auditing occurs at designated time points (i.e., annually) and involves the review of a determined percentage of the enrolled participants in moderate and low-risk trials.

The HDFCCC Director appoints the DSMC Chair. The DSMC Chair and DSMC Director, together with the Deputy Director, appoint other voting faculty members of the DSMC. The DSMC Vice Chair is also appointed by the DSMC Chair and Deputy Director and serves as the DSMC Chair in instances where there is Conflict of Interest (COI) or when the DSMC Chair is out of the office. The DSMC voting faculty members generally serve in the committee for renewable two year terms and may serve indefinitely, as there is not a term limit. DSMC members are listed in Appendix D. The DSMC meets every eight 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 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 DSMC Auditor Supervisor, the DSMC Education and Training Manager, and all Junior and Senior Data and Safety Auditors (indirectly through the DSMC Auditor Supervisor) in the DSMC. Both the Junior and Senior Data and Safety Auditor (DSA) positions report directly to the DSMC Auditor Supervisor, who reports to the DSMC Administrative Director (Appendix B).

3.7 Membership

DSMC faculty membership reflects the composition of HDFCCC clinical investigators and is composed of experienced clinical investigators. The HDFCCC biostatistics shared resource (BIOST) provides a biostatistician as a standing, voting member of the DSMC. If the BIOST member assigned to the DSMC is involved in any capacity with the development of a study under DSMC review, the BIOST provides an alternate biostatistician on an *ad hoc* basis. Membership on the DSMC faculty committee consists of renewable 2-year terms and may serve indefinitely, as there is not a term limit.

The DSMC faculty membership includes Associate or Assistant level professors with at least 2 years of experience as a faculty member (instructor level or higher) and who have previously served or are currently serving as a PI on at least one investigator-initiated or industry-sponsored study as of the date of DSMC appointment. Early Career Investigators who do not meet this criteria may serve on the DSMC but are required to receive training and mentorship by the DSMC Chair and Vice Chairs and DSMC Director during the first 2 years of service. All DSMC faculty members receive onboarding training by the DSMC Director (or designee) prior to serving on the DSMC.

3.8 DSMC Meetings

DSMC meetings occur on every 8-week basis and require at least a majority (greater than 50%) attendance by the voting faculty DSMC members in order for voting and decisions to be determined. The meetings include a review and approval of minutes from the previous meeting, review and approval of DSMB reports, protocol reviews, IRB determinations, SAE and death on study adjudications, as well as a review of monitoring visit reports.

3.8.1 Phase I Trials and Pilot/Dose-Finding Trials

Phase I and other dose-finding trials are monitored prior to the requested dose escalation or expansion 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 for the entirety of the Dose Limiting Toxicity (DLT) window until the Maximum Tolerated Dose ensure adequate time allocation for monitoring. Additionally, a dose escalation/expansion or safety lead-in report (Appendices K and L) will need to be completed and submitted to the DSMC Chair for review and approval. Once the dosing cohort has completed enrollment and is evaluable, the DSMC Chair (or designee) reviews the PI's submitted request and completed DSMC Monitoring Visit Report (MVR) and Action Item Report (AIR) for that cohort. For Conflict of Interest (COI) concerns (i.e., if the DSMC Chair is the PI or a Sub-Investigator on the trial being reviewed) or in situations whereby the DSMC Chair is absent/unavailable (e.g., vacation (MTD) is determined. The DLT window generally is within 28 days to 6 months in length. Once the MTD is determined for the expansion cohort, then the trial is audited on an annual basis for the remainder of the study, with a random selection participants selected for review at the MTD or lower dose levels and audited through the first three cycles of treatment, or until participant discontinuation, whichever is earlier. A total of 20% of the enrolled number of participants at UCSF and at least one participant from each participating site (if the study is a multicenter or consortia study) is reviewed in the expansion cohort until enrollment closure and no active participants on treatment and all participants are in survival follow-up and off treatment.

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), including Consent Incident and Privacy Incident, reviews), as well as audit/inspection preparation will continue until enrollment closure and no active participants on treatment and all participants are in survival follow-up and off treatment.

3.8.2 Vaccine and Gene Therapy Trials

Vaccine and gene therapy trials are monitored on a quarterly basis, regardless of the 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 high-risk 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, including Consent Incident and Privacy Incident, reviews), and audit/inspection preparation will continue until enrollment closure and no active participants on treatment and all participants are in survival follow-up and off treatment.

3.8.3 Phase II, III, and IV Trials

Phase II, III, and IV therapeutic trials are audited on an annual basis, with all data from a random selection of enrolled participants selected of these annual reviews. For single site Phase 2 studies, a total of 20% of the enrolled participants is audited for these studies through the first three cycles of treatment, with no more than a total of 10 participants reviewed Monitoring visits will occur until enrollment closure and no active participants on treatment and all participants are in survival follow-up and off treatment.. For multicenter and consortia studies, a total of 20% of the enrolled participants at UCSF will be audited through the first three cycles of treatment, with at least one participant at each participating site UCSF will be audited through the first three cycles of treatment until enrollment closure and no active participants on treatment and all participants are in survival follow-up and off treatment. If the Phase II/III trial has a safety lead-in cohort, then the DSMC will provide monitoring of all participants in this cohort, through the DLT window or pre-specified safety lead-in window, prior to submission of a safety lead-in report by the study team to the DSMC Chair or Vice Chair for approval. After the safety lead-in request is granted by the DSMC Chair (or designee), the trial is then audited on

an annual basis with a random selection of participants reviewed until enrollment closure or if the study is in the process of data analysis. Regulatory reviews of the trial, safety reviews (i.e., SAE reviews and PV, including Consent Incident and Privacy Incident, reviews), and audit/inspection preparation will continue until enrollment closure or if the study is in the process of data analysis.

3.8.4 Dose Escalations and Safety Lead-In Reviews

For dose escalation and safety lead-in requests, the study team should notify the DSMC Director approximately 4 weeks in advance of expected dose escalation or cohort expansion (i.e., at the time of consent of the final patient expected to complete a given dosing cohort) to 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 MVR, AIR, and the dose 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.

3.8.5 Institutional Protocol Reviews

The DSMC must perform a review of all Institutional trial protocols prior to submission to the PRMC to ensure that the correct DSMP auditing or monitoring template has been incorporated into the protocol. A formal signed DSMC approval letter will be provided to the study team prior to submission of the protocol to the PRMC.

3.8.6 International Trials

As per the HDFCCC Policy on Minimum Standards for Partnerships with International Clinical Research Organizations, the Primary PI or Coordinating Center must utilize and contract with an international Clinical Research Organization (CRO) or other monitoring entity for the monitoring and auditing of non-US participating sites. CCCROC and the DSMC must approve the choice of the CRO or monitoring entity and their monitoring SOPs. The CRO or monitoring entity must provide the monitoring or auditing report for the DSMC's review within 5 business days of the completion of the monitoring report. In general, the DSMC will not provide monitoring/auditing services for international trials conducted by a HDFCCC PI; however, with DSMC Chair (or designee) and Director 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.

3.8.7 Non-Therapeutic Trials

For greater than minimal risk non-therapeutic trials, the assigned DSA will audit the entire chart for at least one enrolled participant 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. Regulatory reviews of the trial, safety reviews (i.e., SAE reviews and PV reviews), and audit/inspection preparation (as applicable) will continue until study closure.

3.8.8 Minimal Risk Trials

For minimal risk non-therapeutic trials, only SAEs entered n OnCore will be reviewed at each DSMC meeting for these trials, with safety reviews (i.e., SAE reviews and PV, including Consent Incident and Privacy Incident reviews), and audit/inspection preparation will continue until

enrollment closure or if the study is in the process of data analysis.

3.8.9 Consortia Trials (non-UCSF PI)

For Consortia Trials with a non-UCSF PI, the DSMC will agree to provide auditing/monitoring services for the HDFCCC site only and will follow the HDFCCC NCI-approved DSMP when reviewing the HDFCCC site. The HDFCCC DSMC will provide auditing/monitoring visit reports to the non-UCSF PI for review within 20 business days of completing the auditing/monitoring.

3.8.10 Regulatory Audits

An abbreviated regulatory review (i.e., review of protocol and consent versions, SAEs, PVs, Delegation of Authority (DOA) logs, FDA Form 1572 forms, etc.) will occur at each participant monitoring review for above minimal risk trials only; however, a full regulatory review will occur on a biennial basis by the DSMC for regulatory compliance for all above minimal risk trials (Appendix G). Regulatory audits will occur until enrollment closure and no active participants on treatment and all participants are in survival follow-up and off treatment.

3.8.11 Monitoring Visit Reports (MVRs)

MVRs and Action Item Reports (AIR) are sent to the study team for follow-up review and action item resolution. These reports are then formally reviewed at the DSMC Committee meeting following the monitoring and auditing visit. The DSA will send both an MVR and an AIR to the study team within 1 calendar month after the monitoring visit is complete for the study team to resolve all action items from the AIR report within 8 weeks. The due date for the completion of the action items may be extended for up to two additional 1-month extensions for extenuating circumstances, if approved by the DSMC Director. Additionally, the AIR report must be completed by the study team prior to the next dose escalation or cohort expansion request (Appendix F). Monitoring visits will occur until enrollment closure and no active participants on treatment and all participants are in survival follow-up and off treatment.

3.8.12 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 the trial, or an Investigator's research portfolio, or a study program until a robust corrective and preventative action plan (CAPA) is developed by the 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 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).

3.8.13 Protocol Violation and Consent Incident Reviews

All Protocol Violations (PVs) and Consent and Privacy Incidents that occur in any cancer trial are reviewed by the DSMC (and the CRSO Associate Director, Clinical Research Programs, for CRSO-specific trials) to ensure that a root cause analysis has been completed and that there is an adequate and feasible corrective and preventative action (CAPA) plan in place. After the study teams have submitted the PV or Consent/Privacy Incident Report to the IRB, the IRB will then determine if the report will need to be reviewed by the full IRB Panel. If the IRB Committee

determines that the PV, Consent, or Privacy Incident Report meets the criteria for a Serious Noncompliance or Serious and Continuing Noncompliance determination, then DSMC is notified of this determination. This report is then submitted to either the FDA (for trials with an Investigational New Drug (IND) application) or the UCSF Office of Ethics and Compliance (for trials without an IND).

4 Data and Safety Monitoring Plan (DSMP) Templates

4.1 Required Elements

All institutional clinical trials conducted at the UCSF HDFCCC must have a satisfactory DSMP template consistent with the 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).

5 Guidelines for Data and Safety Monitoring Implementation

The PI (or study team designee) will conduct a review of data integrity and patient safety at Site Committee meetings. Phase I trials will undergo weekly review; Phase II, III, and IV trials will undergo at least a monthly review. Discussion and conclusions will be documented in the Site Committee meeting minutes, which are stored in the study team's shared file. 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).

6 Implementation of Reporting Requirements

6.1 Adverse Event and Serious Adverse Event (SAE) Reporting

- The DSMC reviews all grade(s) 1-5 adverse events (AEs), regardless of causality, relationship, and expectedness to the treatment, device, and study procedure for Phase I trials and all grade(s) 3-5 AEs, regardless of causality, relationship, and expectedness to the study treatment, device, and study procedure for Phase II, III, and IV trials, including non-therapeutic trials, when reviewing institutional studies. The DSMC may also review grade 1 and 2 AEs for Phase II and III trials as per protocol (i.e., events of special interests). These AEs are tracked in OnCore as per the table below.
- The DSMC reviews and adjudicates 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 study treatment, device, and study procedure procedures must be reported by the PI to the DSMC Chair or designee within one business day of study team awareness.
- SAEs 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 to IP or study procedures	SAEs	SAEs
2	Grade 3-5 AEs, regardless of causality and relationship to IP or study procedures.	SAEs	SAEs
3	Grade 3-5 AEs, regardless of causality and relationship to IP or study procedures	SAEs	SAEs
4	Grade 3-5 AEs, regardless of causality and relationship to IP or study procedures	SAEs	SAEs
Non-Therapeutic	Grade 3-5 AEs, only if related to study procedures	SAEs	SAEs

- The 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.

6.2 Serious Adverse Event (SAE) Review and Adjudication Process

As per section 6 (Implementation of Reporting Requirements) of the DSMP, the DSMC is responsible for reviewing and adjudicating all Serious Adverse Events (SAE), which includes all Deaths on Study, regardless of the relationship to the Investigational Product (IP), Investigational Device (ID), or Research Procedure (RP). The Principal Investigator (PI) and research teams from the HDFCCC and participating sites are required to enter all SAEs regardless of attribution in OnCore. The HDFCCC coordinating and participating sites are responsible for alerting the DSMC Chair (or Vice Chair) and Administrative Director via e-mail if there are any Deaths on Study that are related to the IP, ID, or RP within one business day.

The PI and study team should include the following in the narrative of the Death on Study submitted to the IRB: date/time of awareness of the SAE event (along with explanation and Note to File with Correction and Preventative Action Plan for any instances of delayed reporting), disease diagnosis, name/class of the Investigative Product or Device, last date of treatment, the investigator's assessment of relationship and expectedness of the Death on Study to the IP, ID, or RP, and an adequate summary of the events from this Death on Study. The PI and the study team should provide any necessary supporting documents (i.e., hospitalization records) as requested to the DSMC Chair (or Vice Chair) and DSMC Administrative Director if needed for review of this Death on Study. The DSMC Chair (or Vice Chair) and DSMC Administrative Director inquire with the PI if there are any follow-up questions, including the rationale for the relatedness of the event. The DSMC ensures that the PI and study team have reported all related Deaths on Study to the UCSF IRB and the FDA (if the event is deemed unexpected), and the Company providing the IP or ID (if applicable).

The DSMC Administrative Director runs an SAE Report from OnCore (including related and unrelated) prior to the DSMC Committee Meetings and ensures that all necessary information as noted above is included in the reports from the PI and the study teams. The information from the DSMC OnCore Report is added to the SAE Report Summary document, which includes an overview of the total number of SAEs (including the number of each grade of SAEs),

relatedness status, the narrative information for each Death on Study, and summary information regarding each related SAE. The OnCore SAE Report and the SAE Report Summary are reviewed and signed by the DSMC Chair (or Vice Chair) and reviewed at the DSMC Committee meeting to ensure that the Committee members are in agreement with the relatedness and expectedness of the SAEs. If there are any questions from the Committee members, then the PI and the study team will be contacted to confirm the rationale of relationship and/or expectedness of the SAE to the IP, ID, or RP. The DSMC Administrative Director will confirm with the PI and the study team have submitted all related SAEs to the IRB, FDA (if unexpected), and the Sponsor (if applicable).

6.3 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 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.

7 Monitoring Procedure

The Data and Safety Auditor (DSA) manages the logistics associated with the monitoring review sessions. Once the clinical trial is identified for review, the DSA 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 DSA reviews the regulatory files on a biennial basis and uses online remote platforms to review the following:

- 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 alternative CTMS system).
    - 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.

    - All versions of the 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.
- Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, and Available (ALCOA +)
- 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 DSA will complete the MVR and AIR (see Appendix F, G, H, and I), which describes the findings of this monitoring visit. The study is given an overall evaluation by the DSA, review and approved by the DSMC Monitor and 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 serious noncompliance determinations with notification of the PRMC and IRB. The follow-up response and CAPA are due to the DSMC Director within 10 business days. The DSMC Chair or designee will notify the IRB and PRMC within 10 business days regarding this determination.
- **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 and the PRMC within 10 business days regarding this determination.

8 Data Quality Control

8.1 Pre-Industry Sponsored Audit and Pre-Regulatory Agency Inspection

The DSMC will conduct a trial review prior to Industry-Sponsored Quality Assurance Audit. Additionally, the DSMC will conduct pre-FDA Inspection Reviews 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 DSA 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 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 or Consent and Privacy Incidents with a CAPA.

8.2 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 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 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 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 trial.

8.3 Conflict of Interest

The voting members of the DSMC or DSMB must recuse themselves from discussion during the DSMC/B meetings for any review of their trials in which they are an Investigator, or in instances

whereby the DSMC and B member(s) (or relevant family members, especially if they are a study staff member in the trial) have any financial interests in the trial being discussed.

The DSMC Chair or Vice 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 Site Committee. Instead, one of the other DSMC Vice Chairs is required to review and sign the monitoring report, as well as approve any dose escalation or safety lead-in reports.

9 HDFCCC Data and Safety Monitoring Board (DSMB) Guidelines

9.1 Membership

a) Nonvoting members, (i.e., HDFCCC DSAs) of the DSMB will perform auditing and monitoring activities of all multicenter and consortium trials.

b) Faculty voting members of the DSMB will be the same voting members of the DSMC.

9.2 Meeting Procedures

a) Frequency

   i. Yearly DSMB reports for all Multicenter and Consortium trials will be reviewed at DSMB Meetings.

   ii. DSMB meetings occur as part of the regularly scheduled DSMC meetings (i.e., every 8 weeks)

   iii. Annual DSMB reports will occur for institutional multicenter and consortia studies until all participants are off treatment and in survival follow-up.

b) Elements for Review

   i. The annual DSMB report will be scheduled by the DSMC Director from the DSMB Review schedule in the DSMC Share drive. The faculty member of the DSMC selected for this review must be provided with at least 2 weeks to review this trial.

   ii. The DSMC Director (or designee) will develop the formal annual DSMB report (see Appendix E) for the DSMC Chair or Vice Chair's review and the report will be reviewed at the next DSMC meeting by a selected faculty DSMB member not affiliated with the trial.

   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.

9.3 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.

f) The DSMB reports will be provided to the study team after all required signatures from the DSMB faculty reviewer, the DSMC Chair (or Vice Chair), and the DSMC Director have signed the DSMB report after review at the DSMB meeting.

9.4 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.

9.5 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.

10 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 continual education with regards to clinical research in the UCSF HDFCCC of all clinical research staff, including Investigators, clinical research coordinators and nurses, protocol project managers (PPMs), and Regulatory team members at all campuses of UCSF, including the partner sites in the San Francisco Bay Area.

Investigators: All UCSF and UCSF HDFCCC regional partner site Investigators who are conducting cancer related studies are required, as per the HDFCCC Data and Safety Monitoring Plan (DSMP) and the HDFCCC Investigator Training Policy, to complete the formal HDFCCC investigator training prior to conducting any study-specific procedures for trials in which they are listed as an Investigator. This includes all Advanced Practice Providers, including Nurse Practitioners (NP) and Physician Assistants (PA). The Site Committee is responsible for ensuring the PI has completed the required training during the initial study review, and notifying the HDFCCC DSMC ETO if the training has not been completed. The DSMC ETO will assign the HDFCCC Investigator training module to the Investigator through the UC Learning portal. The Investigator will receive weekly reminder notifications via e-mail until the training has been completed. The Investigator must complete the initial training prior to conducting trials on which they are listed as an Investigator. If the Investigator does not complete the initial required training (and required refresher training), then the DSMC will review and determine remediation steps necessary to ensure completion of this required training. This may include mandating a hold on accrual for all studies being conducted by the PI. Investigators who are listed as Sub-Is and have not yet completed the initial or refresher training will not be able to initiate or continue work on the trial(s) until this training has been completed.

All Investigators are required to complete the refresher every 3 years. Investigators will receive an automated notification of the requirement to complete this retraining within 60 calendar days

of the expiry of their training period. Investigators will continue to receive this automated e-mail notification on a weekly basis until the training has been completed. The DSMC ETO will also receive these notifications and will follow-up with the Investigators if the 3-year training certification timeline has expired to ensure that this training is completed. If the investigator refresher training has not been completed after a month of the expiration of their initial or refresher training, then the DSMC will review and determine necessary remediation steps necessary to ensure completion of this required training. This remediation may include mandating a hold on accrual for all studies being conducted by the PI. Investigators who are listed as Sub-Is and have not yet completed the refresher training will not be able to initiate or continue work on the trial(s) until this training has been completed.

The DSMC ETO will track initial and refresher training for all Investigators conducting cancer related clinical research. The DSMC ETO will follow-up with the Investigators who are delinquent in this training to remind them of potential remediation steps necessary to ensure completion of this required training. The DSMC ETO will provide a listing from UC Learning of the Investigator Training status on a weekly basis, which will highlight which Investigators have lapsed training. All PIs and Sub-Investigators cannot open a new trial or continue to work on the trial until the initial and/or refresher training has been completed.

After completion of the training, Investigators will receive a link to a Qualtrics Survey to provide their feedback on the training, noting recommendations for future topics of training, effectiveness of current training, and follow-up questions from the training. The DSMC ETO will follow-up with any Investigator who has additional questions after the training. The other results from the survey will be utilized for modifications and additions to the current training.

The initial investigator training was rolled out in 2016, but the investigator refresher training was not available until June 2023, so the greater than 3-year delay in the refresher training for all applicable Investigators was due to the delay in the development and approval of this refresher training.

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 HDFCCC CRC onboarding series is offered every month and is required for all new Clinical Research Coordinators (CRCs), Clinical Research Supervisors (CRSs), and Clinical Research Managers (CRMs) conducting cancer clinical research trials. The module courses are offered in-person and include the following topics:

- **Introductory Courses**
    - Intro to Clinical Research
    - Intro to Oncology
    - Research Job Overview
    - Introduction to DSMC
    - Introduction to Investigator Initiated Trials
    - CRC Overview of Adult Infusion Center (offered every two months)
- **Core Courses**
    - Protocol Training
    - Informed Consent
    - Study Coordination Part 1 – Screening
    - Study Coordination Part 2 – Eligibility

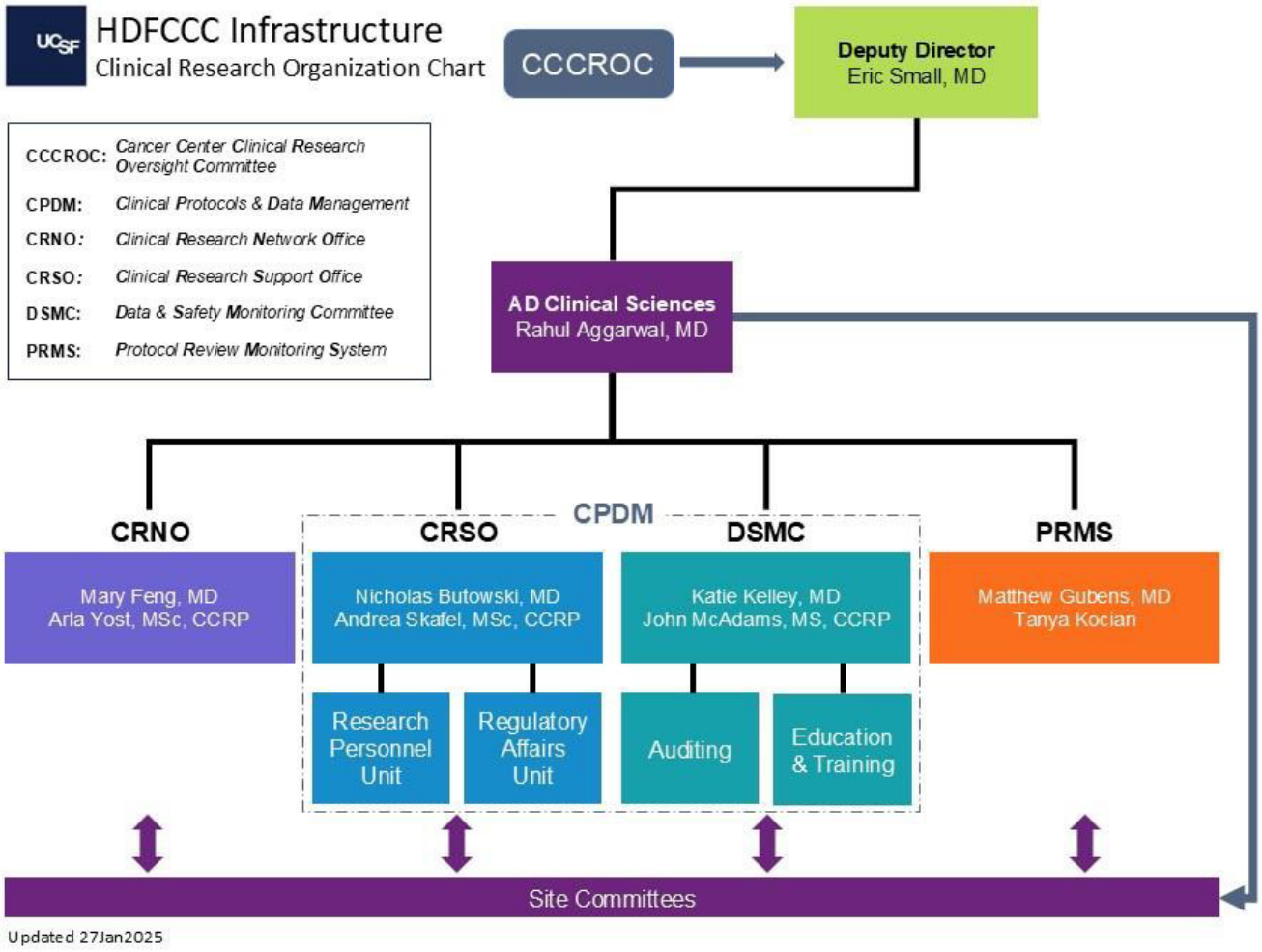
- Adverse Event and Serious Adverse Event
- Notification of New Risk & Re-consent
- Protocol Deviations and Violations
- Data & Monitoring Visit
- Billing and Finance
- Patient Travel Reimbursement (recording)

****A final quiz is administered once all core courses (excluding the patient travel reimbursement course) have been completed.*

- **Continuing Education Courses** (offered to expand the skill set of a clinical research support staff and are taught remotely via Zoom)
    - **Mandatory Courses**
        - Consenting for non-therapeutic trials
            - Mandatory for CRCs, RNs, or other research staff who will obtain informed consent for non-therapeutic trials
            - Also, reviews how to consent for non-English-speaking participants
        - Communication and Health Literacy
            - Mandatory for all staff who are participant-facing.
        - Cooperative Group (only mandatory for staff who work on a cooperative group trial)
    - **Optional Courses**
        - Audit and Inspection Readiness
        - Implicit/Unconscious Bias
        - Managing Challenging Patient Behaviors
    - **Regulatory Courses** (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
        - New Trial Start Up (Industry Sponsored) Amendments (Externally Sponsored Studies)
        - Regulatory Binder
        - Study Closeout with IRB
        - Expanded Access
        - Investigator Initiated Study Start-up
        - PPM Introduction to Protocol Development
        - CRSO Central Regulatory Introduction for Study Teams (Externally Sponsored Studies)

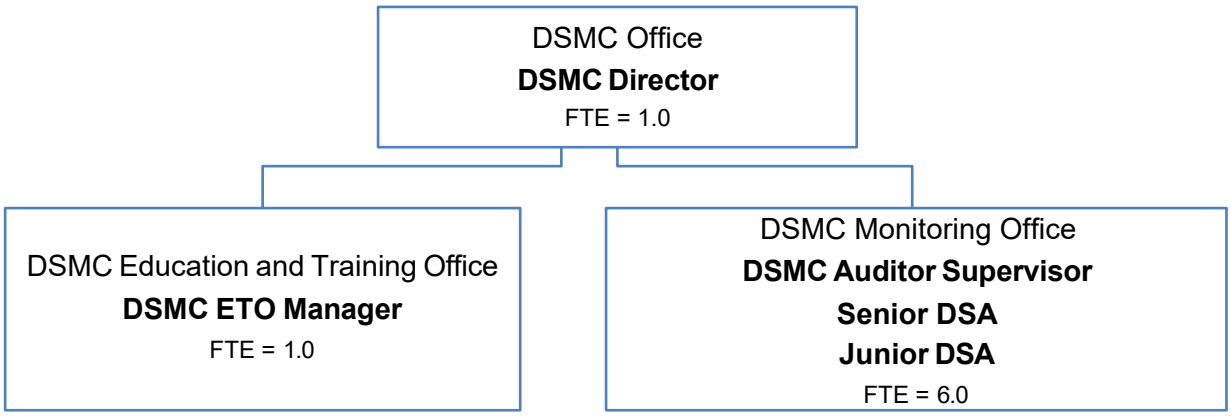
Appendix A. HDFCCC Clinical Trials Infrastructure

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 (Auditing and Education and Training) and their staff managers and personnel.



Appendix C. UCSF HDFCCC Site Committees and Chairs

Site Committee	Chair
Breast Oncology	John Park, MD
Cancer Immunotherapy Program (CIP)	Peter Sayre, MD
Cancer and Tobacco Control (CTC)	Scarlett Gomez and Tung Nguyen, MD
Cutaneous Oncology	Jason Chan, MD
Experimental Therapeutics Department	Pamela Munster, MD
Gastrointestinal Oncology	Katie Kelley, MD
Genitourinary Oncology	Rahul Aggarwal, MD
Gynecologic Oncology	Edwin Alvarez, MD
Hematopoietic Oncology (Adult)	Thomas Martin, MD
Molecular Imaging and Radionuclide Therapy	Thomas Hope, MD
Neurologic Oncology	Nicholas Butowski, MD
Oral, Head & Neck Oncology	Alain Algazi, MD
Pediatric Oncology	Alyssa Reddy, MD
Radiation Oncology	Mary Feng, MD
Survivorship and Symptom Science	Niharika Dixit, MD
Thoracic Oncology	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	Professor
Jennie Taylor, MD	Vice Chair and Neurologic Oncology	Associate Professor
Amanda Marinoff, MD**	Pediatric Oncology	Assistant Professor
Weiyun Ai, MD	Hematologic Oncology	Professor
Vadim Koshkin, MD	Genitourinary Oncology	Assistant Professor
Collin Blakely, MD	Thoracic Oncology	Associate Professor
Steve Braunstein, MD	Radiation Oncology	Associate Professor
Edwin Alvarez, MD	Gynecologic Oncology	Professor
Spencer Behr, MD	MIRT*	Associate Professor
Fei Jiang, PhD	Biostatistics Core	Professor
Kelli Walker, PharmD	Investigational Drug Service	Assistant Professor

**Molecular Imaging and Radionuclide Therapy*

***Early Career Investigator (Mentored Role)*

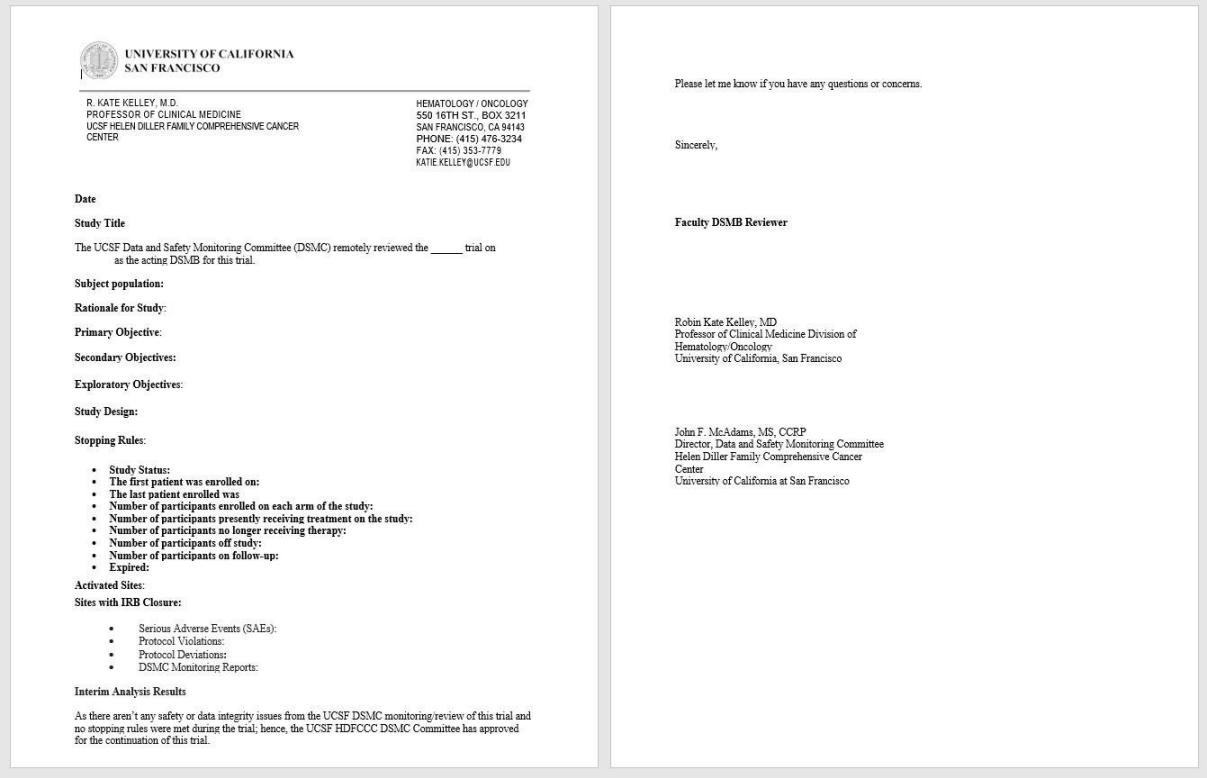
Data and Safety Monitoring & Education and Training Office Non-Voting Members

John F. McAdams, MS, CCRP	DSM Director
Melody Gawliu, BA, CCRP	DSM Auditor Supervisor
Amy Li, MPA, CCRP	DSM Education and Training Manager
Marvin Bolanos, BS, CCRP	DSM Senior DSA*
Hazel Dias, BS, CCRP	DSM Senior DSA*
Avic Magsaysay, MD, CCRP	DSM CRNO Senior DSA*
Nela Pawlowska, MD, CCRP	DSM Senior DSA*
Jian Fang, BS, CCRP	DSM Senior DSA*

**Data & Safety Auditor*

Appendix E. DSMB Report Template

DSMB Report Template (version 28



UNIVERSITY OF CALIFORNIA
SAN FRANCISCO

R. KATE KELLEY, M.D.
PROFESSOR OF CLINICAL MEDICINE
UCSF HELEN DILLER FAMILY COMPREHENSIVE CANCER CENTER

HEMATOLOGY / ONCOLOGY
550 16TH ST., BOX 3211
SAN FRANCISCO, CA 94143
PHONE: (415) 476-3234
FAX: (415) 353-7779
KATIE.KELLEY@UCSF.EDU

Date

Study Title

The UCSF Data and Safety Monitoring Committee (DSMC) remotely reviewed the _____ trial on as the acting DSMB for this trial.

Subject population:

Rationale for Study:

Primary Objective:

Secondary Objectives:

Exploratory Objectives:

Study Design:

Stopping Rules:

- **Study Status:**
- **The first patient was enrolled on:**
- **The last patient enrolled was**
- **Number of participants enrolled on each arm of the study:**
- **Number of participants presently receiving treatment on the study:**
- **Number of participants no longer receiving therapy:**
- **Number of participants off study:**
- **Number of participants on follow-up:**
- **Expired:**

Activated Sites:

Sites with IRB Closure:

- Serious Adverse Events (SAEs):
- Protocol Violations:
- Protocol Deviations:
- DSMC Monitoring Reports:

Interim Analysis Results

As there aren't any safety or data integrity issues from the UCSF DSMC monitoring/review of this trial and no stopping rules were met during the trial; hence, the UCSF HDFCCC DSMC Committee has approved for the continuation of this trial.

Please let me know if you have any questions or concerns.

Sincerely,

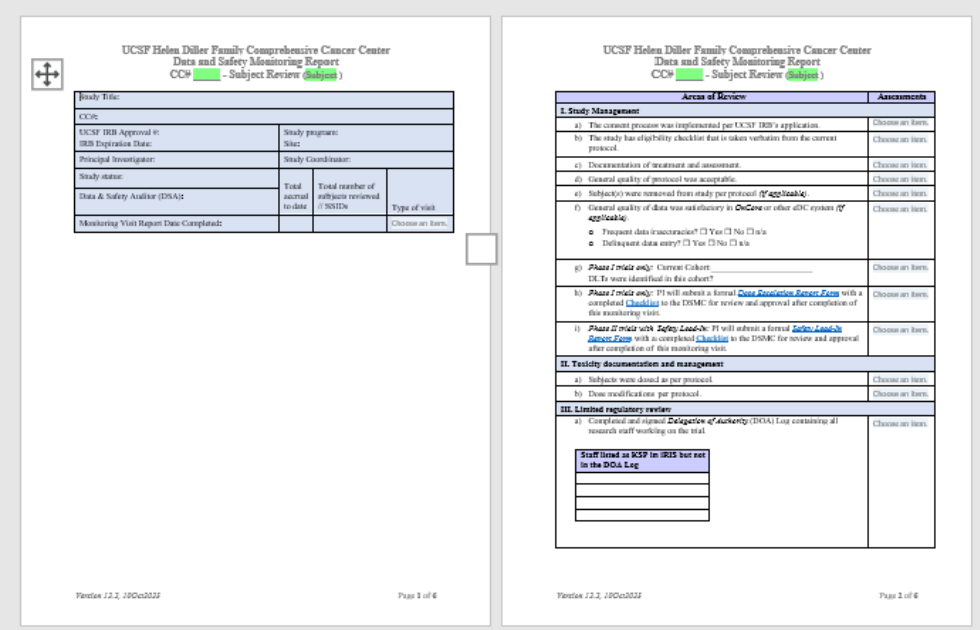
Faculty DSMB Reviewer

Robin Kate Kelley, MD
Professor of Clinical Medicine Division of Hematology/Oncology
University of California, San Francisco

John F. McAdams, MS, CCRP
Director, Data and Safety Monitoring Committee
Helen Diller Family Comprehensive Cancer Center
University of California at San Francisco

Appendix F. Data and Safety Monitoring Reports: Subject Monitoring Report (version 10Jan2024)

DSMC Subject Monitoring Report (v



UCSF Helen Diller Family Comprehensive Cancer Center
Data and Safety Monitoring Report
CC# ____ - Subject Review (Subject)

Study Title:			
CC#:			
UCSF IRB Approval #: IRB Expiration Date:	Study program: Site:		
Principal Investigator:	Study Coordinator:		
Study status: Data & Safety Auditor (DSA):	Total accrual to date	Total number of subjects reviewed // SSIDs	Type of visit
Monitoring Visit Report Date Completed:			Choose an item.

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UCSF Helen Diller Family Comprehensive Cancer Center
Data and Safety Monitoring Report
CC# ____ - Subject Review (Subject)

Areas of Review	Assessments
I. Study Management	
a) The consent process was implemented per UCSF IRB's application.	Choose an item.
b) The study has eligibility checklist that is taken verbatim from the current protocol.	Choose an item.
c) Documentation of treatment and assessment.	Choose an item.
d) General quality of protocol was acceptable.	Choose an item.
e) Subject(s) were removed from study per protocol *(if applicable)*.	Choose an item.
f) General quality of data was satisfactory in *OnCore* or other eDC system *(if applicable)*: ▪ Frequent data inaccuracies? ☐ Yes ☐ No ☐ n/a ▪ Delinquent data entry? ☐ Yes ☐ No ☐ n/a	Choose an item.
g) *Phase I trials only*: Current Cohort: _____ DLTs were identified in this cohort?	Choose an item.
h) *Phase I trials only*: PI will submit a formal Dose Escalation Report Form with a completed Checklist to the DSMC for review and approval after completion of this monitoring visit.	Choose an item.
i) *Phase II trials with Safety Lead-In*: PI will submit a formal Safety Lead-In Report Form with a completed Checklist to the DSMC for review and approval after completion of this monitoring visit.	Choose an item.
II. Toxicity documentation and management	
a) Subjects were dosed as per protocol.	Choose an item.
b) Dose modifications per protocol.	Choose an item.
III. Limited regulatory review	
a) Completed and signed *Delegation of Authority* (DOA) Log containing all research staff working on the trial. **Staff listed as KSP in iRIS but not in the DOA Log**	Choose an item.

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UCSF Helen Diller Family Comprehensive Cancer Center
Data and Safety Monitoring Report
CC# ____ - Subject Review (Subject)

b) Completion of both the FDA Form(s) 1571 and FDA 1572 *(for IND held IITs)* or FDA Form(s) 1572 *(for non-IND held IITs or Industry Sponsored Trials (ISTs))*? ▪ Does the FDA 1572 reconcile with the DOA log? ☐ Yes ☐ No ☐ n/a	Choose an item.
c) The Financial Disclosure Forms (FDFs – Form 3454 and 3455) were completed for all applicable staff on the FDA 1572 Form.	Choose an item.
Comments regarding regulatory review:	

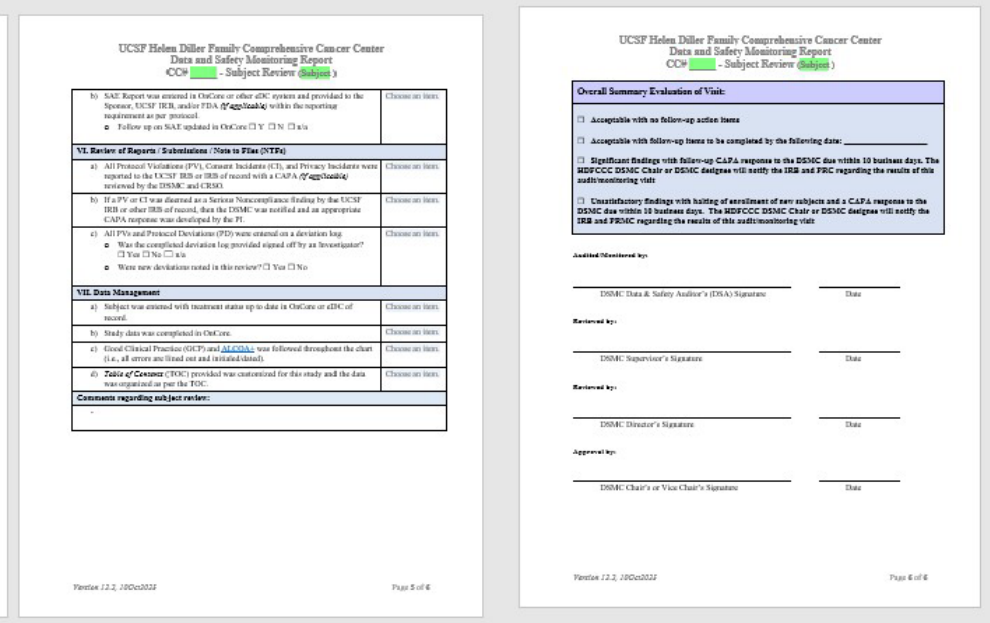
Subject Review		
Subject initials:	Subject ID #:	
Visits/Dates Monitored:	Subject's Current Status:	
Areas of Review		**Assessments**
I. Informed Consent		
a) Subject consented with correct ICF version with all required signatures by *Key Study Personnel* (KSP). ▪ HIPAA and ISOR signed ☐ Y ☐ N ▪ Person obtaining consent signed after patient/parent/guardian ☐ Y ☐ N ☐ unknown ▪ HDFCCC Informed Consent Policy and HDFCCC Consent Guideline followed correctly ☐ Y ☐ N ▪ Person obtaining consent delegated on DOA Log ☐ Y ☐ N ▪ Consent process documented ☐ Y ☐ N ☐ Preferred ☐ Short-form ☐ n/a ▪ *For non-English speakers*, which consenting process was used: ☐ Preferred ☐ Short-form ☐ n/a ▪ A reconsent took place ☐ Y ☐ N ☐ n/a		Choose an item.
b) New risk(s) communicated with subject as per HDFCCC Safety Reporting Policy *(if applicable)*: ▪ Documentation of new risk(s) communicated to subject either verbally or via reconsent ☐ Y ☐ N ▪ Subject notified verbally or reconsented in a timely manner as per HDFCCC Policy ☐ Y ☐ N		Choose an item.
II. Eligibility		

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UCSF Helen Diller Family Comprehensive Cancer Center
Data and Safety Monitoring Report
CC# ____ - Subject Review (Subject)

a) All screening and pretreatment procedures were completed and signed by investigator in a timely manner. ▪ Medical History form completed ☐ Y ☐ N ☐ n/a ▪ Baseline Conditions Log completed ☐ Y ☐ N ☐ n/a ▪ Concomitant Medications (Con-Med) Log completed ☐ Y ☐ N	Choose an item.
b) Subject eligibility confirmed with supporting documentation for each inclusion and exclusion criterion. ▪ Eligibility Packet organized and the data in each report, dictation or form relating to the eligibility criteria found on Eligibility Checklist is highlighted or flagged ☐ Y ☐ N ▪ Investigator signed and dated all screening source documents and all abnormal findings assessed for clinical significance ☐ Y ☐ N ▪ Investigator signed and dated each page of Eligibility Checklist ☐ Y ☐ N ▪ Eligibility Checklist signed and dated by the Investigator, CRC, and CRM (or delegate) ☐ Y ☐ N ▪ Eligibility Checklist completed after subject consented ☐ Y ☐ N	Choose an item.
III. Treatment	
a) Treatment per protocol confirmed. ▪ MAR ☐ Y ☐ N ☐ n/a ▪ Pill diary ☐ Y ☐ N ☐ n/a ▪ DARFs for Oral Meds ☐ Y ☐ N ☐ n/a ▪ *If subject was non-compliant with taking oral meds*, is there documentation of recounseling? ☐ Y ☐ N ☐ n/a ▪ Infusion Orders ☐ Y ☐ N ☐ n/a ▪ Dose modifications ☐ Y ☐ N ☐ n/a ▪ OK to Treat Forms ☐ Y ☐ N ☐ n/a	Choose an item.
IV. Assessment	
a) All assessments completed per protocol. ▪ Lab Report(s) reviewed, marked for clinical significance, graded if applicable, signed, and dated ☐ Y ☐ N ☐ n/a	Choose an item.
b) Disease response assessment completed per protocol *(if applicable)*: ☐ Y ☐ N ☐ n/a	Choose an item.
V. Adverse Event (AE) and Serious Adverse Event (SAE)	
a) AEs and SAEs were confirmed with source documentation. ▪ Reviewed, marked for clinical significance, graded, expectedness, action taken, attribution ☐ Y ☐ N ☐ n/a ▪ Signed in a timely manner ☐ Y ☐ N ☐ n/a	Choose an item.

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UCSF Helen Diller Family Comprehensive Cancer Center
Data and Safety Monitoring Report
CC# ____ - Subject Review (Subject)

b) SAE Report was entered in OnCore or other eDC system and provided to the Sponsor, UCSF IRB, and/or FDA *(if applicable)* within the reporting requirement as per protocol. ▪ Follow up on SAE updated in OnCore ☐ Y ☐ N ☐ n/a	Choose an item.
VI. Review of Reports / Submissions / Note to Files (NTFs)	
a) All Protocol Violations (PV), Consent Incidents (CI), and Privacy Incidents were reported to the UCSF IRB or IRB of record with a CAPA *(if applicable)* reviewed by the DSMC and CRSO.	Choose an item.
b) If a PV or CI was disarmed 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.
c) All PVs and Protocol Deviations (PD) were entered on a deviation log. ▪ Was the completed deviation log provided signed off by an Investigator? ☐ Yes ☐ No ☐ n/a ▪ Were new deviations noted in this review? ☐ Yes ☐ No	Choose an item.
VII. Data Management	
a) Subject was entered with treatment status up to date in OnCore or eDC of record.	Choose an item.
b) Study data was completed in OnCore.	Choose an item.
c) Good Clinical Practice (GCP) and ALCOA+ was followed throughout the chart (i.e., all errors are lined out and initialed/dated).	Choose an item.
d) ***Table of Contents*** (TOC) provided was customized for this study and the data was organized as per the TOC.	Choose an item.
Comments regarding subject review:	
-	

Version 12.2, 10Oct2023 Page 5 of 6

UCSF Helen Diller Family Comprehensive Cancer Center
Data and Safety Monitoring Report
CC# ____ - Subject Review (Subject)

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 PRMC regarding the results of this audit/monitoring visit**

Audited/Monitored by:

_____ _____
DSMC Data & Safety Auditor's (DSA) Signature Date

Reviewed by:

_____ _____
DSMC Supervisor's Signature Date

Reviewed by:

_____ _____
DSMC Director's Signature Date

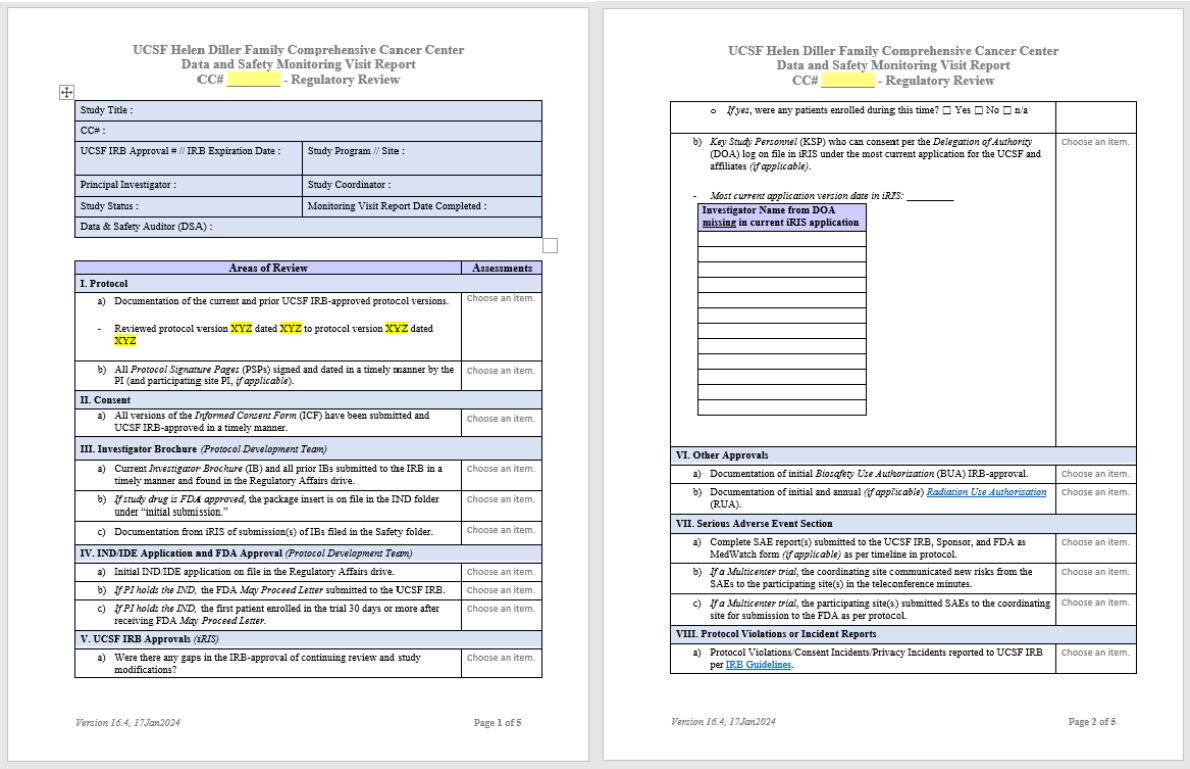
Approved by:

_____ _____
DSMC Chair's or Vice Chair's Signature Date

Version 12.2, 10Oct2023 Page 6 of 6

Appendix G. Data and Safety Monitoring Reports: Regulatory Monitoring Report (version 17Jan2024)

DSMC Regulatory Monitoring Report (v



UCSF Helen Diller Family Comprehensive Cancer Center
Data and Safety Monitoring Visit Report
CC# _____ - Regulatory Review

Study Title :	
CC# :	
UCSF IRB Approval # // IRB Expiration Date :	Study Program // Site :
Principal Investigator :	Study Coordinator :
Study Status :	Monitoring Visit Report Date Completed :
Data & Safety Auditor (DSA) :	

Areas of Review	Assessments
I. Protocol	
a) Documentation of the current and prior UCSF IRB-approved protocol versions. - Reviewed protocol version XYZ dated XYZ to protocol version XYZ dated XYZ	Choose an item.
b) All *Protocol Signature Pages* (PSPs) signed and dated in a timely manner by the PI (and participating site PI, *if applicable*).	Choose an item.
II. Consent	
a) All versions of the *Informed Consent Form* (ICF) have been submitted and UCSF IRB-approved in a timely manner.	Choose an item.
III. Investigator Brochure *(Protocol Development Team)*	
a) Current *Investigator Brochure* (IB) and all prior IBs submitted to the IRB in a timely manner and found in the Regulatory Affairs drive.	Choose an item.
b) *If study drug is FDA approved*, the package insert is on file in the IND folder under "initial submission."	Choose an item.
c) Documentation from iRIS of submission(s) of IBs filed in the Safety folder.	Choose an item.
IV. IND/IDE Application and FDA Approval *(Protocol Development Team)*	
a) Initial IND/IDE application on file in the Regulatory Affairs drive.	Choose an item.
b) *If PI holds the IND,* the FDA *May Proceed Letter* submitted to the UCSF IRB.	Choose an item.
c) *If PI holds the IND,* the first patient enrolled in the trial 30 days or more after receiving FDA *May Proceed Letter.*	Choose an item.
V. UCSF IRB Approvals *(iRIS)*	
a) Were there any gaps in the IRB-approval of continuing review and study modifications?	Choose an item.

Version 16.4, 17Jan2024 Page 1 of 5

UCSF Helen Diller Family Comprehensive Cancer Center
Data and Safety Monitoring Visit Report
CC# _____ - Regulatory Review

o *If yes*, were any patients enrolled during this time? ☐ Yes ☐ No ☐ n/a	
b) *Key Study Personnel* (KSP) who can consent per the *Delegation of Authority* (DOA) log on file in iRIS under the most current application for the UCSF and affiliates *(if applicable)*. - *Most current application version date in iRIS:* _____ **Investigator Name from DOA missing in current iRIS application**	Choose an item.
VI. Other Approvals	
a) Documentation of initial *Biosafety Use Authorization* (BUA) IRB-approval.	Choose an item.
b) Documentation of initial and annual *(if applicable)* *Radiation Use Authorization* (RUA).	Choose an item.
VII. Serious Adverse Event Section	
a) Complete SAE report(s) submitted to the UCSF IRB, Sponsor, and FDA as MedWatch form *(if applicable)* as per timeline in protocol.	Choose an item.
b) *If a Multicenter trial*, the coordinating site communicated new risks from the SAEs to the participating site(s) in the teleconference minutes.	Choose an item.
c) *If a Multicenter trial*, the participating site(s) submitted SAEs to the coordinating site for submission to the FDA as per protocol.	Choose an item.
VIII. Protocol Violations or Incident Reports	
a) Protocol Violations/Consent Incidents/Privacy Incidents reported to UCSF IRB per IRB Guidelines.	Choose an item.

Version 16.4, 17Jan2024 Page 2 of 5

IX. Study Personnel Documents

a) All Key Study Personnel (KSP) have CITI Training (GCP and HSP) up to date. — Choose an item.

- *The following KSP have missing or expired CITI Training:*

KSP	GCP expiration date	HSP expiration date

b) Documentation of training for the initial protocol and all amendments for all staff on the Delegation of Authority (DOA) Log filed in the regulatory files. — Choose an item.

- *The following KSP have missing protocol documentation:*

KSP	Training documentation missing for the following protocol versions

c) Completed and signed Delegation of Authority (DOA) Log containing all research staff working on the trial. — Choose an item.

Staff listed as KSP in iRIS but not in the DOA Log	Staff listed as KSP in DOA Log but not in iRIS

d) Curriculum Vitae (CV) for all Investigators and up to date licenses for all MDs and NPs. — Choose an item.

- *The following Investigators have CVs or Licenses that are expired or missing:*

Investigator Name	Missing CV	MD/NP License Expiration Date

e) Completion of both the FDA Form(s) 1571 and FDA 1572 *(for IND held IITs)* or FDA Form(s) 1572 *(for non-IND held IITs or Industry Sponsored Trials (ISTs))*? — Choose an item.
- Does the FDA 1572 reconcile with the DOA log? ☐ Yes ☐ No ☐ n/a

f) The Financial Disclosure Forms (FDFs – Form 3454 and 3455) were completed for all applicable staff on the FDA 1572 Form. — Choose an item.

X. Laboratory Documentation

a) *For research specific labs listed on the FDA 1572*, CLIA certifications, CAPs, laboratory normal reference ranges, and the CV(s) and lab license(s) of the Lab Director(s) were provided. — Choose an item.

- *The following are laboratories which have missing documentation marked with an 'X.' If it was provided, it is marked with 'n/a'*

Laboratory name	CLIA	CAP	Lab Director Name	CV	ML

Comments regarding regulatory 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 PRMC regarding the results of this audit/monitoring visit**

Audited/Monitored by:

_____ _____
DSMC Data & Safety Auditor's (DSA) Signature Date

Reviewed by:

_____ _____
DSMC Supervisor's Signature Date

Reviewed by:

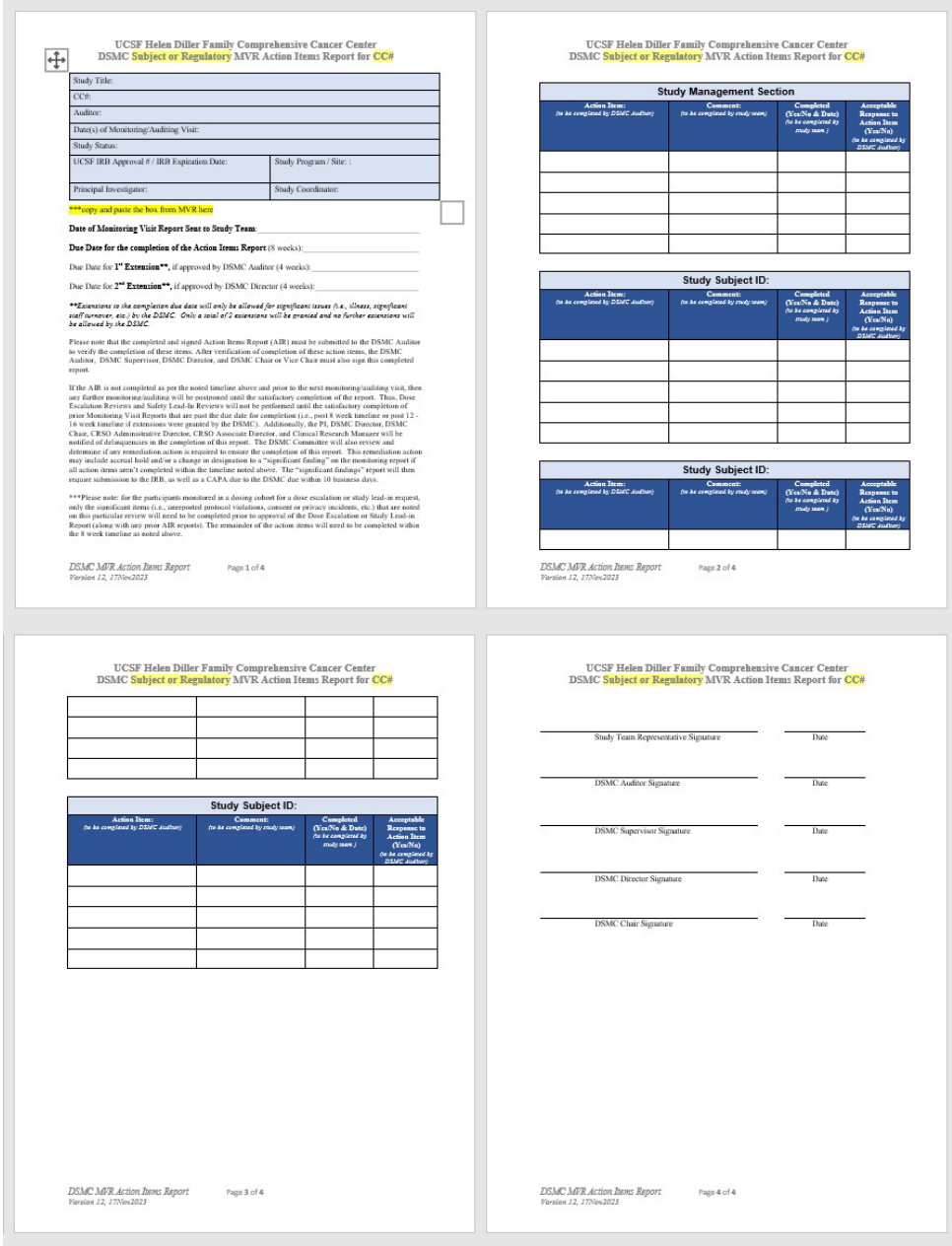
_____ _____
DSMC Director's Signature Date

Approval by:

_____ _____
DSMC Chair's or Vice Chair's Signature Date

Appendix H. Subject or Regulatory Action Item Report (AIR) (version 17Nov2023)

DSMC Subject or Regulatory MVR Action Items Report (AIR)



UCSF Helen Diller Family Comprehensive Cancer Center
DSMC Subject or Regulatory MVR Action Items Report for CC#

Study Title:	
CC#:	
Auditor:	
Date(s) of Monitoring/Auditing Visit:	
Study Status:	
UCSF IRB Approval # / IRB Expiration Date:	Study Program / Site: :
Principal Investigator:	Study Coordinator:

***copy and paste the box from MVR here

Date of Monitoring Visit Report Sent to Study Team:_____

Due Date for the completion of the Action Items Report (8 weeks):_____

Due Date for **1st Extension****, if approved by DSMC Auditor (4 weeks):_____

Due Date for **2nd Extension****, if approved by DSMC Director (4 weeks):_____

***Extensions to the completion due date will only be allowed for significant issues (i.e., illness, significant staff turnover, etc.) by the DSMC. Only a total of 2 extensions will be granted and no further extensions will be allowed by the DSMC.*

Please note that the completed and signed Action Items Report (AIR) must be submitted to the DSMC Auditor to verify the completion of these items. After verification of completion of these action items, the DSMC Auditor, DSMC Supervisor, DSMC Director, and DSMC Chair or Vice Chair must also sign this completed report.

If the AIR is not completed as per the noted timeline above and prior to the next monitoring/auditing visit, then any further monitoring/auditing will be postponed until the satisfactory completion of the report. Thus, Dose Escalation Reviews and Safety Lead-In Reviews will not be performed until the satisfactory completion of prior Monitoring Visit Reports that are past the due date for completion (i.e., past 8 week timeline or past 12 - 16 week timeline if extensions were granted by the DSMC). Additionally, the PI, DSMC Director, DSMC Chair, CRSO Administrative Director, CRSO Associate Director, and Clinical Research Manager will be notified of delinquencies in the completion of this report. The DSMC Committee will also review and determine if any remediation action is required to ensure the completion of this report. This remediation action may include accrual hold and/or a change in designation to a "significant finding" on the monitoring report if all action items aren't completed within the timeline noted above. The "significant findings" report will then require submission to the IRB, as well as a CAPA due to the DSMC due within 10 business days.

***Please note: for the participants monitored in a dosing cohort for a dose escalation or study lead-in request, only the significant items (i.e., unreported protocol violations, consent or privacy incidents, etc.) that are noted on this particular review will need to be completed prior to approval of the Dose Escalation or Study Lead-in Report (along with any prior AIR reports). The remainder of the action items will need to be completed within the 8 week timeline as noted above.

DSMC MVR Action Items Report Page 1 of 4
Version 12, 17Nov2023

UCSF Helen Diller Family Comprehensive Cancer Center
DSMC Subject or Regulatory MVR Action Items Report for CC#

Study Management Section

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

Study Subject ID:

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

Study Subject ID:

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

DSMC MVR Action Items Report Page 2 of 4
Version 12, 17Nov2023

UCSF Helen Diller Family Comprehensive Cancer Center
DSMC Subject or Regulatory MVR Action Items Report for CC#

Study Subject ID:

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

DSMC MVR Action Items Report Page 3 of 4
Version 12, 17Nov2023

UCSF Helen Diller Family Comprehensive Cancer Center
DSMC Subject or Regulatory MVR Action Items Report for CC#

Study Team Representative Signature _____ Date _____

DSMC Auditor Signature _____ Date _____

DSMC Supervisor Signature _____ Date _____

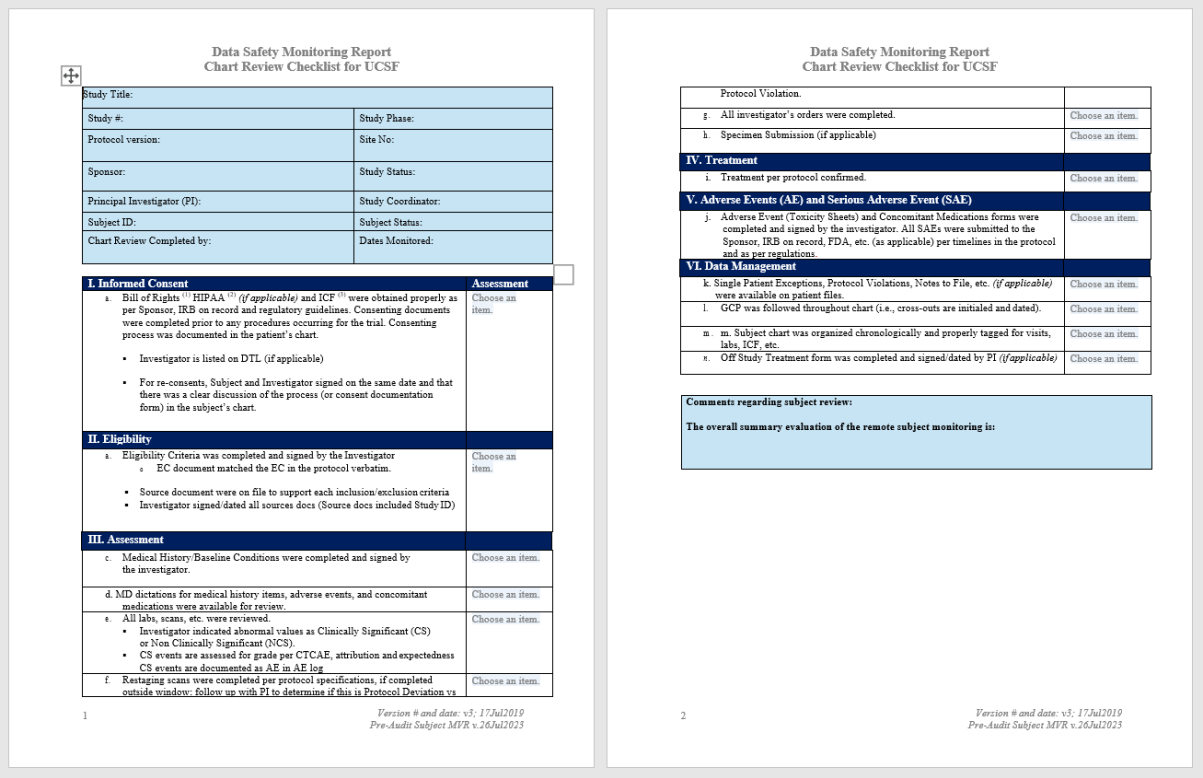
DSMC Director Signature _____ Date _____

DSMC Chair Signature _____ Date _____

DSMC MVR Action Items Report Page 4 of 4
Version 12, 17Nov2023

Appendix I. DSMC CRNO Chart Review Checklist for UCSF and Affiliates (version 02Oct2023)

DSMC Pre-Audit Review of UCSF Trials



Data Safety Monitoring Report
Chart Review Checklist for UCSF

Study Title:	
Study #:	Study Phase:
Protocol version:	Site No:
Sponsor:	Study Status:
Principal Investigator (PI):	Study Coordinator:
Subject ID:	Subject Status:
Chart Review Completed by:	Dates Monitored:

I. Informed Consent	Assessment
a. Bill of Rights [1] HIPAA [2] *(if applicable)* and ICF [3] 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. ▪ Investigator is listed on DTL (if applicable) ▪ 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.	Choose an item.
II. Eligibility	
a. Eligibility Criteria was completed and signed by the Investigator o EC document matched the EC in the protocol verbatim. ▪ Source document were on file to support each inclusion/exclusion criteria ▪ Investigator signed/dated all sources docs (Source docs included Study ID)	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. ▪ Investigator indicated abnormal values as Clinically Significant (CS) or Non Clinically Significant (NCS). ▪ CS events are assessed for grade per CTCAE, attribution and expectedness CS events are documented as AE in AE log	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	Choose an item.

1 *Version # and date: v3; 17Jul2019 Pre-Audit Subject MVR v.26Jul2023*

Data Safety Monitoring Report
Chart Review Checklist for UCSF

Protocol Violation.	
g. All investigator's orders were completed.	Choose an item.
h. Specimen Submission (if applicable)	Choose an item.
IV. Treatment	
i. Treatment per protocol confirmed.	Choose an item.
V. Adverse Events (AE) and Serious Adverse Event (SAE)	
j. 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.
VI. Data Management	
k. Single Patient Exceptions, Protocol Violations, Notes to File, etc. *(if applicable)* were available on patient files.	Choose an item.
l. GCP was followed throughout chart (i.e., cross-outs are initialed and dated).	Choose an item.
m. m. Subject chart was organized chronologically and properly tagged for visits, labs, ICF, etc.	Choose an item.
n. Off Study Treatment form was completed and signed/dated by PI *(if applicable)*	Choose an item.

Comments regarding subject review:

The overall summary evaluation of the remote subject monitoring is:

2 *Version # and date: v3; 17Jul2019 Pre-Audit Subject MVR v.26Jul2023*

Appendix J. DSMC Dose Escalation/Expansion Report (version 12Mar2024)



DSMC Dose Escalation_Expansion

Principal Investigator: Date:

DSMC Dose Escalation/Expansion Report

STUDY TITLE: CC#

1. *Give a brief summary of the trial from the protocol.*

a) **Treatment Regimen or Cohort Levels**
Put in graphic or flow sheet form.

b) **Objectives:**
   a. **Primary Objectives:**
   b. **Secondary Objectives:**
   c. **Exploratory Objectives**

c) **Dose Limiting Toxicities (list from protocol):**

d) **Stopping Rules:**
   - Efficacy
   - Safety

2) **ENROLLMENT STATUS**
Example,
- Date first participant treated.
- X enrolled to date
- X receiving treatment on trial to date
- X off study (indicate which cycle):
  - X withdrew consent
  - X off-study 2° to toxicity
  - X off-study for disease progression

DSMC Dose Escalation/Expansion Report
Version 12Mar2024

Principal Investigator: Date:

- X off study for completion of study/completion of required follow-up

3) PRELIMINARY RESULTS:

a. Safety

Cohort	Participant #/ ID	Dose Level	Date Enrolled	# Cycles completed	Any dose reductions	DLT	Missed Doses of IP	% of IP Dose Received	Comments

b. Participant Evaluability for Cohort

Subject #/ ID	The participant completed the DLT period	Participant met criteria for DLT-evaluability	Comments
	YES ☐ No ☐		
	YES ☐ No ☐		
	YES ☐ No ☐		

d) Summary of AE/SAEs:

This can be a report of all AEs on study or limited to Grade 3 and higher AEs and SAEs and unexpected AEs

e) Patient Discontinuations

Participant ID	Date off Study	Reason for Discontinuation	
#			
#			

DSMC Dose Escalation/Expansion Report
Version 12Mar2024

Principal Investigator: Date:

4) PRELIMINARY DATA: Efficacy (IF APPLICABLE)

Subject Study ID					
Best Response					
# of cycles to date					

Dose Escalation/Expansion Request
Please indicate the dose escalation/expansion request and provide rationale:

Principal Investigator's Signature_____ Date_____

☐ The DSMC Chair/Vice Chair has reviewed the dose escalation report and approves for the study team to move forward with the participant(s) enrollment in the next dose level.

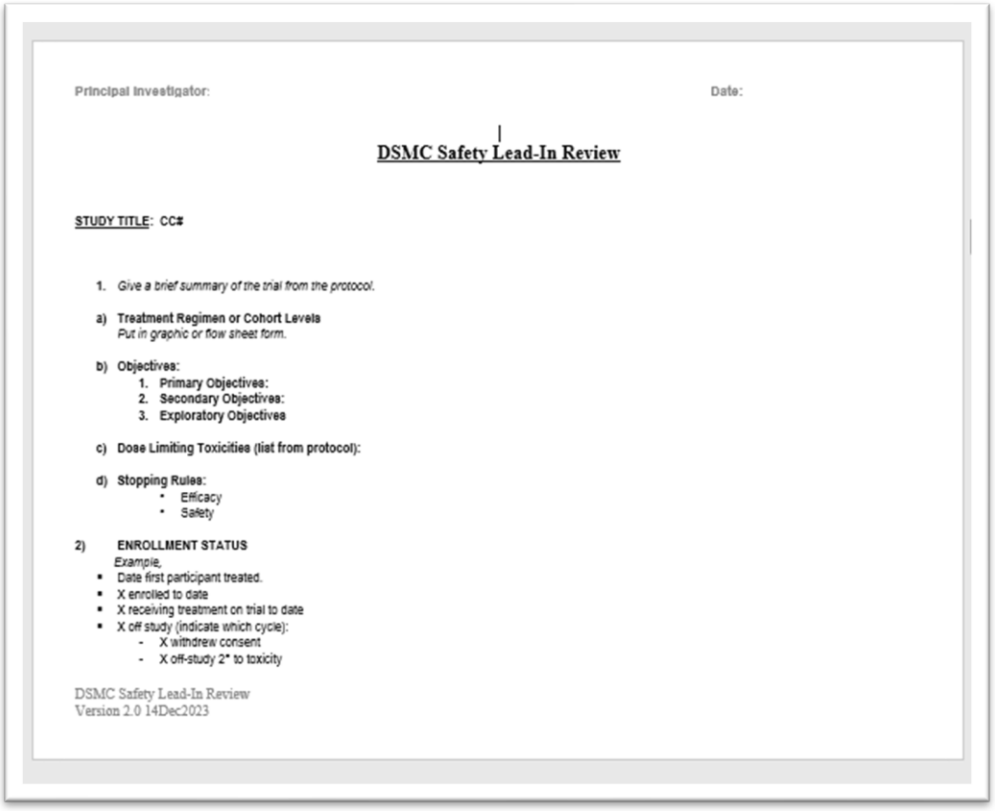
☐ The DSMC Chair/Vice Chair has reviewed the dose escalation report and approves for the study team to move forward with the participant(s) enrollment for the dose expansion cohort (if applicable).

DSMC Chair/Vice Chair Signature of Approval_____ Date_____

DSMC Dose Escalation/Expansion Report
Version 12Mar2024

Appendix K. DSMC Safety Lead-In Report (version 14Dec2023)

DSMC Safety Lead-In Report (v. 14Dec2023



Principal Investigator: Date:

DSMC Safety Lead-In Review

STUDY TITLE: CC#

1. *Give a brief summary of the trial from the protocol.*

a) **Treatment Regimen or Cohort Levels**
Put in graphic or flow sheet form.

b) **Objectives:**
1. **Primary Objectives:**
2. **Secondary Objectives:**
3. **Exploratory Objectives**

c) **Dose Limiting Toxicities (list from protocol):**

d) **Stopping Rules:**
- Efficacy
- Safety

2) **ENROLLMENT STATUS**
Example,
- Date first participant treated.
- X enrolled to date
- X receiving treatment on trial to date
- X off study (indicate which cycle):
  - X withdrew consent
  - X off-study 2° to toxicity

DSMC Safety Lead-In Review
Version 2.0 14Dec2023

Principal Investigator: Date:

- X off-study for disease progression
- X off study for completion of study/completion of required follow-up

3) **PRELIMINARY RESULTS:**

a. **Safety**

Cohort	Participant #/ ID	Dose Level	Date Enrolled	# Cycles completed	Any dose reductions	DLT	Missed Doses of IP	% of IP Dose Received	Comments

b. **Participant Evaluability for Cohort**

Subject #/ ID	The participant completed the DLT period	Participant met criteria for DLT-evaluability	Comments
	YES ☐ No ☐		
	YES ☐ No ☐		
	YES ☐ No ☐		

d) **Summary of AE/SAEs:**
This can be a report of all AEs on study or limited to Grade 3 and higher AEs and SAEs and unexpected AEs

e) **Patient Discontinuations**

Participant ID	Date off Study	Reason for Discontinuation	
#			
#			

Principal Investigator: Date:

4) **PRELIMINARY DATA: Efficacy (IF APPLICABLE)**

Subject Study ID					
Best Response					
# of cycles to date					

Study Lead-in Request
Please indicate the reason for this request (i.e., opening the next arm of the study, etc.)

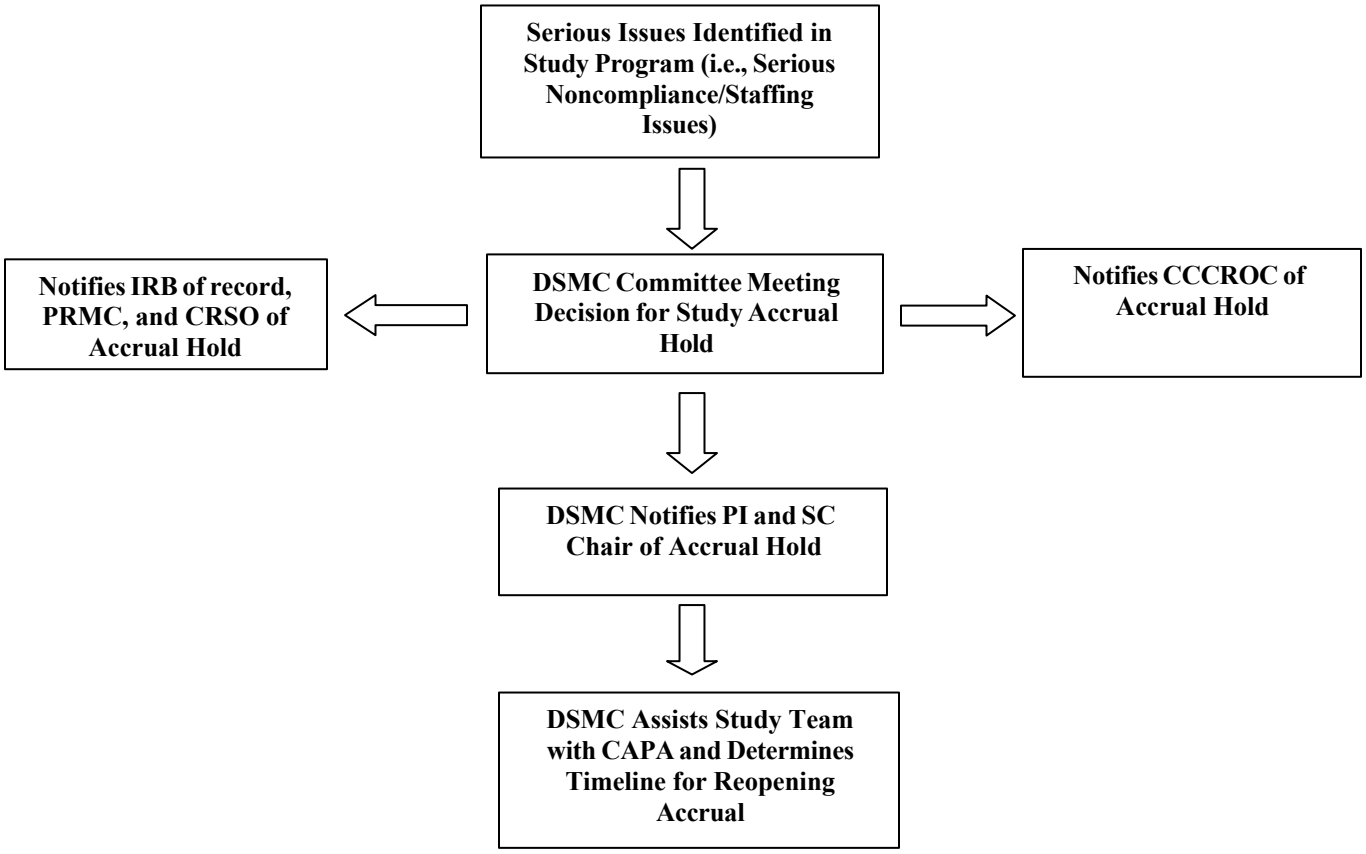
Principal Investigator's Signature_____ Date_____

☐ The DSMC Chair/Vice Chair has reviewed the safety lead-in report and approves for the study team to move forward with the participant(s) enrollment in the next treatment arm,

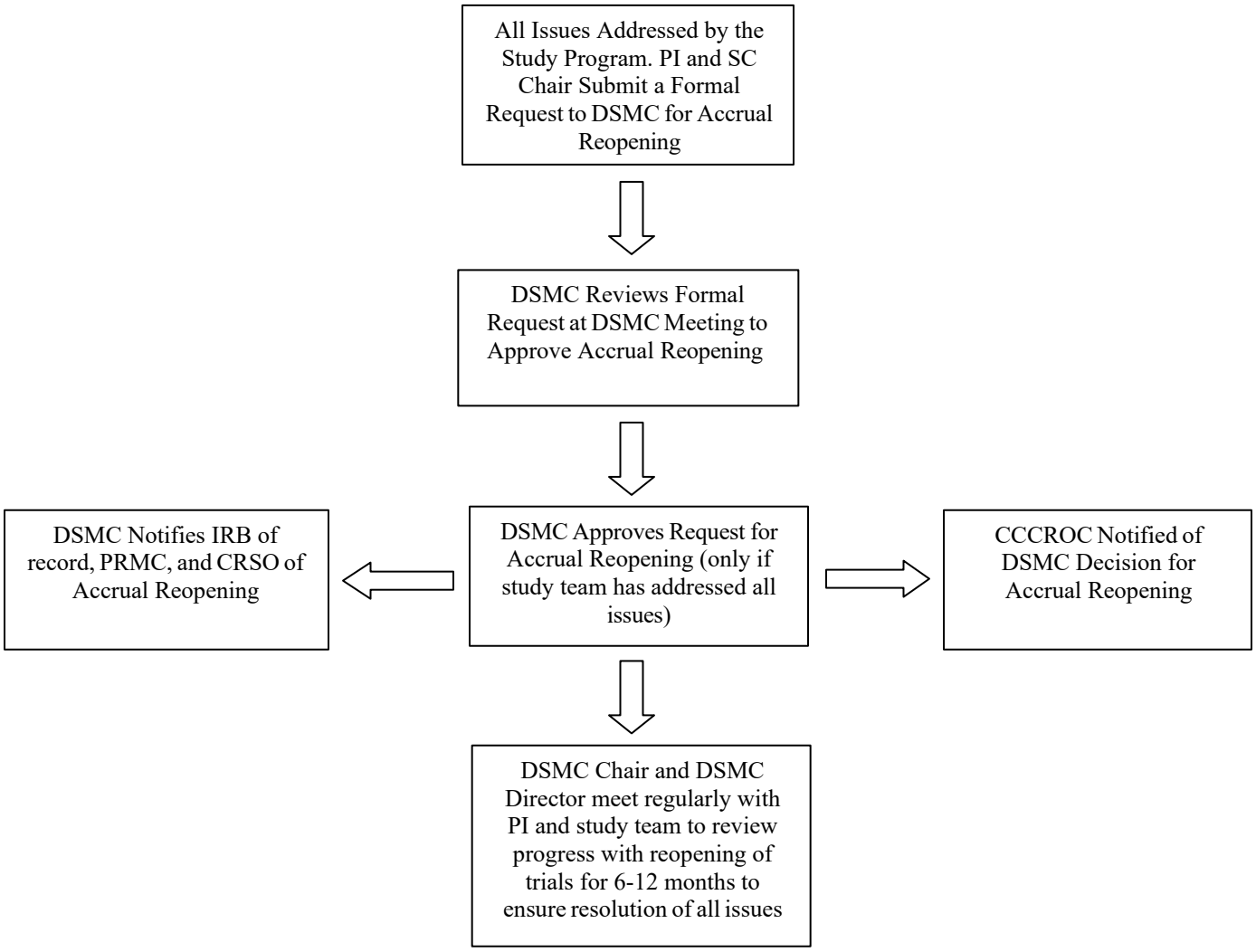
DSMC Chair/Vice Chair Signature of Approval_____ Date_____

DSMC Safety Lead-In Review
Version 2.0 14Dec2023

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



Appendix M. DSMC Remediation Process: Study Program Accrual Reopening



Appendix N. DSMP Templates for Investigators to Insert into IIT Protocols

Note to Investigators: These plans are templates for protocol preparation. Please see the latest version of the DSMP templates on the DSMC section of the HDFCCC website.

Appendix N.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 requested dose escalations
- Review of participant data in each dosing 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 therapeutic dose escalation Phase I trials are generally designated with a high-risk assessment; therefore, the source documents for all enrolled participants in each dosing cohort are monitored by a DSMC DSA prior to approval of the dosing cohort. This includes a review of all study information through the first post-Dose Limiting Toxicity period (DLT period) visit of the trial up until the maximum tolerated dose (MTD) is determined or for the first cycle of treatment for Rolling Six cohorts. Once the MTD is determined and the cohort expansion phase has started, the DSMC DSA will audit 20 percent of the participants enrolled in this cohort through the first three cycles of treatment for each participant reviewed until study is closed to accrual.

The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 1 calendar month after the monitoring visit is complete for the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended for up to an additional 2 months for extenuating circumstances, if approved by the DSMC. The AIR report must be completed by the study team prior to the next monitoring review of this study. Additionally, the action items from the AIR Report must be deemed answered and complete by the DSA after the report has been submitted by the study team; hence, the completed AIR must be sent to the DSMC by 4 weeks prior to the deadline for the DSA's review and confirmation of these completed action items. If the study team is granted a second extension by the DSMC Director, then the DSA will have 4 weeks after the report has been provided to the DSMC to review and confirm the responses on the AIR.

A limited 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.

Scheduled auditing of participant source documents is complete after all files have been reviewed for three cycles of treatment for 20% of the enrolled participants in this cohort, with no more than 10 total participants reviewed during the course of auditing the expansion cohort. 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 study closure.

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 MedWatch form.

UCSF IRB website for guidance in reporting serious adverse

events: https://irb.ucsf.edu/adverse-event

MedWatch forms and information:

www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore. 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 eight weeks. The date the SAE report 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) or research-related procedure, 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/Expansion 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. Also, if there are AIRs that are past the due date for completions (i.e., post 8 week timeline or post 12-16 week timeline if extensions were granted), then the Dose Escalation/Expansion review will be postponed until these action items are all addressed by the study team.

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.

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Appendix N.2 (Single Site) High-Risk Non-Dose Finding Phase I Trial

Data and Safety Monitoring Plan for a High-Risk Non-Dose Finding Phase I 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 non-dose finding therapeutic trials, are generally designated with a high-risk assessment. The data is monitored by an assigned Data and Safety Auditor (DSA) on a quarterly basis throughout the year (depending on accrual) as participants are enrolled in the trial. Each participant chart is reviewed through the first month of study drug therapy. The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 1 calendar month after the monitoring visit is complete for the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended for up to an additional 2 months for extenuating circumstances, if approved by the DSMC. The AIR report must be completed by the study team prior to the next review of this study. Additionally, the action items from the AIR Report must be deemed answered and complete by the DSA after the report has been submitted by the study team; hence, the completed AIR must be sent to the DSMC by 4 weeks prior to the deadline for the DSA's review and confirmation of these completed action items. If the study team is granted a second extension by the DSMC Director, then the DSA will have 4 weeks after the report has been provided to the DSMC to review and confirm the responses on the AIR.

A limited 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 monitoring of all enrolled participants in these trials has been completed, regulatory reviews, safety reviews (i.e., Serious Adverse Event (SAE) and Protocol Violation (PV) report reviews), and audit/inspection preparation (as applicable) will continue until study closure.

3. Review and Oversight Requirements

a. 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:

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

b. Serious Adverse Event Reporting

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

i. Death,
ii. Life-threatening adverse experience*,
iii. Inpatient hospitalization or prolongation of existing hospitalization,
iv. Persistent or significant disability/incapacity,
v. Congenital anomaly/birth defect, or cancer, or
vi. 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,
vii. 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

All serious adverse events are entered into OnCore. 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 eight weeks. The date the SAE report 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.

c. 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:

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Appendix N.3 (Single Site) Phase II, III, or IV Institutional Trial

Data and Safety Monitoring Plan for a Phase II, III, and IV 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.

The DSMC DSA will audit up to a maximum of three cycles of treatment for each participant selected for the annual audit. Approximately twenty percent of the participants enrolled in the study will be reviewed until the study is closed to accrual. For example, if there are 10 participants enrolled in the trial, then only 2 participants will be required to be reviewed by the DSA.

For 'greater than minimal risk' single-site Phase 2 or 3 institutional non-therapeutic trials, the assigned DSMC DSA will audit approximately 20% of enrolled participants per year (up to a maximum of 3 per year), with a maximum of 10 participant charts audited overall from the start of the study until the study is closed to accrual. For example, if there are 10 participants enrolled in the trial in a given year, two participants (20%) will be reviewed that year. A limited regulatory review will occur at each auditing visit (i.e., review of the approved protocol and ICF versions, along with the Delegation of Authority (DOA) Log, Financial Disclosure Form (FDF), and the FDA 1572 form); however, a complete regulatory review will occur on a biennial basis by the DSMC for regulatory compliance.

The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 1 calendar month after the monitoring visit is complete for the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended for up to an additional 2 months for extenuating circumstances, if approved by the DSMC. The AIR report must be completed by the study team prior to the next monitoring review of this study. Additionally, the action items from the AIR Report must be deemed answered and complete by the DSA after the report has been submitted by the study team; hence, the completed AIR must be sent to the DSMC by 4 weeks prior to the deadline for the DSA's review and confirmation of these completed action items. If the study team is granted a second extension by the DSMC Director, then the DSA will have 4 weeks after the report has been provided to the DSMC to review and confirm the responses on the AIR.

A limited 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. 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 three cycles of treatment (or a total of 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 trial closure.

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

All serious adverse events are entered into OnCore. 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.

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Appendix N.4 (Single Site) Phase II Trial or Pilot Study with Safety Lead-In Phase

Data and Safety Monitoring Plan: Institutional (Single Site) Phase II Trial or Pilot Study 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 the safety lead-in phase by DSMC Chair or Vice Chair
- Annual auditing after completion of the 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 or Pilot 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. However, if there are AIRs that are past the due date for completions (i.e., post 8 week timeline or post 12-16 week timeline if extensions were granted), then the safety lead-in review will be postponed until these action items are all addressed by the study team.

After the completion of enrollment in the safety lead-in phase, the Principal Investigator will submit a report to the DSMC Chair (or Vice Chair) outlining all AEs, SAEs, and DLTs (as defined in the protocol) with a request to proceed onto the next phase of the study. For the Safety Lead-in Cohorts, the HDFCCC PI and study team representative must notify the DSMC once the final participant in the cohort is enrolled in the trial and will be required to complete the DSMC Study Safety Lead-In Report and DSMC Dose Escalation/Expansion and Safety Lead-In Request Checklist. The DSMC Director will review and provide approval on a case by case basis for Dose Escalation review that requires a more

expedited review timeline (i.e., less than 4 weeks' notice). The study team representative must complete the report and checklist and send to the DSMC DSA to review prior to PI's sign off. The DSMC DSA will then review the report for completeness and accuracy, and will submit the completed DSMC Study Safety Lead-In Report, signed and dated by the PI, to the DSMC Chair (or Vice Chair) and Director requesting approval from the DSMC prior to further enrollment in the trial as per protocol. The DSMC Chair (or Vice Chair) will grant approval of this request within 2 business days from receipt from the DSMC DSA if there aren't any significant safety issues (i.e., SAEs, protocol violations, etc.) in the participant cohort that was audited.

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 participants reviewed. The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 1 calendar month after the monitoring visit is complete for the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended up to an additional 2 months for extenuating circumstances if approved by the DSMC. The AIR report must be completed by the study team prior to the next monitoring review of this study. Additionally, the action items from the AIR Report must be deemed answered and complete by the DSA after the report has been submitted by the study team; hence, the completed AIR must be sent to the DSMC by 4 weeks prior to the deadline for the DSA's review and confirmation of these completed action items. If the study team is granted a second extension by the DSMC Director, then the DSA will have 4 weeks after the report has been provided to the DSMC to review and confirm the responses on the AIR.

A limited 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 (or 10 total participants) have been audited through three 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 study closure.

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

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 eight weeks. The date the SAE report 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.

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Appendix N.5 (Single Site) Non-therapeutic Institutional Study

Data and Safety Monitoring Plan for a Non-therapeutic Institutional Study for a Non-Therapeutic Greater than Minimal Risk, Low Risk Category Study

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and participant safety for all HDFCCC institutional clinical trials. This non-therapeutic study of a new diagnostic agent has been determined to be "greater than minimal risk." and low risk. 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 non-therapeutic studies are characterized as low risk studies due to a research component which introduces risk without therapeutic intent (e.g., a study including an invasive procedure such as a biopsy for research purposes), 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" non-therapeutic studies, the assigned Data and Safety Auditor (DSA) will audit up to three participants once per year. A total of 20% of the enrolled participants in the study will be reviewed, with a maximum of ten participant charts reviewed until study closure.

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

After completion of each auditing visit, the DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 1 calendar month after the monitoring visit is complete for the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended for up to an additional 2 months for extenuating circumstances, if approved by the DSMC. The AIR report must be completed by the study team prior to the next auditing review of this study.

Additionally, the action items from the AIR Report must be deemed answered and complete by the DSA after the report has been submitted by the study team; hence, the completed AIR must be sent to the DSMC by 4 weeks prior to the deadline for the DSA's review and confirmation of these completed action items. If the study team is granted a second extension by the DSMC Director, then the DSA will have 4 weeks after the report has been provided to the DSMC to review and confirm the responses on the AIR.

AA limited 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 studies will be complete after 10 enrolled participants have been audited. However, regulatory reviews of the study, safety reviews

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

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs) related to study procedures, whether considered expected or unexpected, 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 studies 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

All serious adverse events are entered into OnCore. 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 eight weeks. The date the SAE report 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.

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Appendix N.6 (Single or Multicenter Site): Non-therapeutic Institutional Study – Minimal Risk

Data and Safety Monitoring Plan for a Minimal Risk Institutional Study

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and participant safety for all HDFCCC institutional clinical trials. This non-therapeutic study has been determined to be "minimal risk." A summary of DSMC activities for this trial includes:

- Review of serious adverse events and protocol violations only.

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for participant safety for all HDFCCC institutional clinical trials. Minimal risk non-therapeutic studies are characterized as studies without risk due to a research component which introduces procedures which don't involve risk to the participants (e.g., a blood draw study).

Safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews) will continue until the study is closed by the IRB. Regulatory reviews will not be performed for minimal risk institutional studies and are only performed for above minimal risk studies.

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.

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

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 eight weeks. The date the SAE report was sent to all required reporting agencies will be documented in OnCore.

If a death occurs during the course of study participation and is determined to be possibly, probably, or definitely related either to the study procedure, the Investigator or his/her designee must notify the DSMC Chair or Vice Chair and DSMC Director within one business day.

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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Appendix N.7 (Multicenter) Non-Therapeutic Multicenter Institutional Study
Data and Safety Monitoring Plan for a Non-therapeutic Institutional Study for a Non-Therapeutic Greater than Minimal Risk, Low Risk Category Study

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

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and participant safety for all HDFCCC institutional clinical trials. This non-therapeutic study of a new diagnostic agent has been determined to be "greater than minimal risk." and low risk. A summary of DSMC activities for this study 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 studies. 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" non-therapeutic studies, the assigned Data and Safety Auditor (DSA) will audit up to three of the enrolled participants once per year with a total of 20% of the total number of participants enrolled in the study at UCSF and at least 1 participant at each participating site. A total of 1 participant per site will be required to be reviewed, unless there are participants enrolled in cohorts that require all participants to be reviewed (i.e., study lead-in or rolling 6 cohorts).

If blood or tissue banking studies 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 studies.

The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 1with one calendar month after the monitoring visit is complete for the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended for up to an additional 2 months for extenuating circumstances, if approved by the DSMC. The AIR report must be completed by the study team prior to the next monitoring review of this study.

Additionally, the action items from the AIR Report must be deemed answered and complete by the DSA after the report has been submitted by the study team; hence, the completed AIR must be sent to the DSMC by 4 weeks prior to the deadline for the DSA's review and confirmation of these completed action items. If the study team is granted a second extension by the DSMC Director, then the DSA will have 4 weeks after the report has been provided to the DSMC to review and confirm the responses on the AIR.

Auditing in these studies will be complete after 20% of the total number of participants enrolled in the trial at UCSF and at least 1 participant at each participating site(s) has been reviewed. A

of 1 participant per site will be required to be reviewed, unless there are participants enrolled in cohorts

that require all participants to be reviewed (i.e., study lead-in or rolling 6 cohorts).

However, regulatory reviews of the study, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the study 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 study. 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 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) related to study procedures, whether considered expected or unexpected, 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 studies 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

All serious adverse events are entered into OnCore. 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 eight 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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Appendix N.8 (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 institutional multicenter therapeutic dose escalation Phase I trials are generally designated with a high-risk assessment; therefore, the source documents for all enrolled participants in each dosing cohort are monitored by a DSMC DSA prior to approval of the dosing cohort. This includes a review of all study information through the first post-Dose Limiting Toxicity period (DLT period) visit of the trial up until the maximum tolerated dose (MTD) is determined or for the first cycle of treatment for Rolling Sic cohorts. Once the MTD is determined and the cohort expansion phase has started, the DSMC DSA will audit up to a maximum of three cycles of treatment for each participant reviewed. The assigned DSA will review approximately 20% of the total number of participants enrolled in the trial at UCSF and at least 1 participant reviewed at each participating site in the dose expansion phase of the study. .

The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 1 calendar month after the monitoring visit is complete for the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended for up to an additional 2 months for extenuating circumstances, if approved by the DSMC. The

AIR report must be completed by the study team prior to the next monitoring review of this study.

Additionally, the action items from the AIR Report must be deemed answered and complete by the DSA after the report has been submitted by the study team; hence, the completed AIR must be sent to the DSMC by 4 weeks prior to the deadline for the DSA's review and confirmation of these completed action items. If the study team is granted a second extension by the DSMC Director, then the DSA will have 4 weeks after the report has been provided to the DSMC to review and confirm the responses on the AIR.

A limited 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 at UCSF and 1 participant from each participating site have been monitored through one cycle 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 study closure.

Multicenter communication

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. The UCSF Coordinating Center and 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 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/Expansion 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. However, if there are AIRs that are past the due date for completions (i.e., post 8 week timeline or post 12-16 week timeline if extensions were granted), then the Dose Escalation/Expansion review will be postponed until these action items are all addressed by the study team.

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

All serious adverse events are entered into OnCore. 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 all, 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 eight weeks. The date the SAE report 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:

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Appendix N.9 (Multicenter) Non-Dose Finding Phase I Multicenter Trial

Data Safety Monitoring Plan for Non-Dose Finding Phase I Multicenter 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 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 non-dose finding high risk Phase I therapeutic trials, regardless of the study phase, are generally designated with a high-risk assessment. The data is monitored by a Data and Safety Auditor (DSA) on a quarterly basis throughout the year as participants are enrolled in the trial. Each participant chart is reviewed through the first month of study drug therapy.

The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 20 business days after the monitoring visit is complete for the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended for up to an additional 2 months for extenuating circumstances, if approved by the DSMC. The AIR report must be completed by the study team prior to the next monitoring review of this study. This due date for the completion of the action items may be extended an additional 2 months for extenuating circumstances approved by the DSMC. The AIR report must be completed by the study team prior to the next review of this study.

Additionally, the action items from the AIR Report must be deemed answered and complete by the DSA after the report has been submitted by the study team; hence, the completed AIR must be sent to the DSMC by 4 weeks prior to the deadline for the DSA's review and confirmation of these completed action items. If the study team is granted a second extension by the DSMC Director, then the DSA will have 4 weeks after the report has been provided to the DSMC to review and confirm the responses on the AIR.

A limited 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 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

All serious adverse events are entered into OnCore. 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 eight weeks. The date the SAE report 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.

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Appendix N.10 (Multicenter) Phase II, III, or IV Trial

Data and Safety Monitoring Plan for a Multicenter Study Phase II, III, or IV 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, III, or IV therapeutic trials are generally designated with a moderate risk assessment. The DSMC DSA will audit up to a maximum of three cycles of treatment for each participant selected for the annual audit. The assigned DSA will review 20% of the total number of participants enrolled in the trial at UCSF and at least 1 participant at each participating site. A total of 1 participant per site will be required to be reviewed, unless there are participants enrolled in cohorts that require all participants to be reviewed (i.e., study lead-in or rolling 6 cohorts).

The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 1 calendar month after the monitoring visit is complete to be completed within 8 weeks. The due date for the completion of the action items may be extended for up to an additional 2 months for extenuating circumstances, if approved by the DSMC. The AIR report must be completed by the study team prior to the next review of this study.

Additionally, the action items from the AIR Report must be deemed answered and complete by the DSA after the report has been submitted by the study team; hence, the completed AIR must be sent to the DSMC by 4 weeks prior to the deadline for the DSA's review and confirmation of these completed action items. If the study team is granted a second extension by the DSMC Director, then the DSA will have 4 weeks after the report has been provided to the DSMC to review and confirm the responses on the AIR.

A limited 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 a total of 20% of enrolled participants have been audited through three 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 study closure.

The participating site's source documents are audited remotely via review of redacted source documents downloaded by the site into the CRA console of OnCore. The DSA will audit up to 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

All serious adverse events are entered into OnCore. 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 eight weeks. The date the SAE report 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.

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Appendix N.11 (Multicenter) Phase II, III, or IV Trial with Safety Lead-In Phase

Data and Safety Monitoring Plan: Multicenter Phase II, III, or IV 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, III, or IV therapeutic studies with a lead-in are generally 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. However, if there are AIRs that are past the due date for completions (i.e., post 8 week timeline or post 12-16 week timeline if extensions were granted), then the safety lead-in review will be postponed until these action items are all addressed by the study team.

After DSMC authorization to enroll beyond the safety lead-in phase is granted, study data is audited by a DSMC Data and Safety Auditor on an annual basis with a random selection of 20% of the total number of participants (no more than 10 participants). The DSMC Data and Safety Auditor will audit a maximum of three cycles of treatment in the participants selected for review until study closure. The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 1 calendar month after completion of the monitoring visit to be completed within 8 weeks. The due date for the completion

of the action items may be extended for up to an additional 2 months for extenuating circumstances, if approved by the DSMC. The AIR report must be completed by the study team prior to the next review of this study. A limited 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. 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 enrolled at UCSF and at least one participant chart from each participating site 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 study closure.

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.

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- **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.

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Med Watch forms and information:

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All serious adverse events are entered into OnCore. 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 eight weeks. The date the SAE report 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 O. Risk Assessment for Institutional Studies

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

Risk assignment	Study type	Monitoring	Surveillance
High	Institutional Phase 1 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 (up to a maximum of 3/year or a total of 10 participants) through first three cycles of therapy, all study staff are required to receive HDFCCC training prior to working on trial.	Real time monitoring of AEs and SAEs weekly at site committees; DSMC monitors SAEs every eight weeks at DSMC Meetings
High	Non-dose finding Phase I Institutional therapeutic	Monitor all participants on a quarterly basis as enrolled through the first cycle of therapy, all study staff are required to receive HDFCCC training prior to working on trial.	Real time monitoring of AEs and SAEs weekly at site committees; DSMC monitors SAEs every eight weeks at DSMC Meetings
Moderate	Institutional Phase II therapeutic	Audit first three cycles of treatment in 20% of study participants (up to a maximum of 10 participants or 3 per year) on an annual basis, all study staff are required to receive HDFCCC training prior to working on trial.	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors SAEs every eight weeks at DSMC Meetings
Moderate	Institutional Phase II therapeutic with Safety Lead-In	Monitor all patients in the safety lead-in cohort, then audit first three cycles of treatment in 20% of study participants (up to a maximum of 3 per year or a total of 10 participants) thereafter on an annual basis, all study staff are required to receive HDFCCC training prior to working on trial.	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors SAEs every eight weeks at DSMC Meetings

Moderate	Institutional Phase III therapeutic	Audit first three cycles of treatment in 20% of participants (up to a maximum of 3 per year or a total of 10 participants) on an annual basis., All study staff are required to receive HDFCCC training prior to working on trial.	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors for SAEs every eight weeks at DSMC Meetings
Moderate	Institutional Phase IV/other therapeutic	Audit a pre-determined number of cycles of treatment	Real time monitoring of AEs and SAEs monthly at

Risk assignment	Study type	Monitoring	Surveillance
		and/or specific time period post-intervention (according to the window of risk for the intervention being studied as pre-defined in protocol) in 20% of participants on an annual basis. All study staff are required to receive HDFCCC training prior to working on trial.	site committees; DSMC monitors for SAEs every eight weeks at DSMC Meetings
Low	Non-therapeutic trials with research specific study procedures that are deemed above minimal risk (i.e., novel tracers for radiology trials)	Audit participants enrolled in trial once per year, with a total of 20% of participants reviewed, up to a maximum of ten total participants overall reviewed. All study staff are required to receive HDFCCC training prior to working on trial.	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors for SAEs every eight weeks at DSMC Meetings
Minimal Risk	Non-therapeutic trials with minimal risk study procedures	Not responsible for auditing, all study staff are required to receive HDFCCC training prior to working on trial.	Real time monitoring of SAEs monthly at site committees; DSMC monitors for SAEs every eight weeks at DSMC Meetings