

HDFCCC Data and Safety Monitoring Protocol Templates

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I. Introduction

UCSF Helen Diller Family Comprehensive Cancer Center Overview

The University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center (HDFCCC) is a National Cancer Institute (NCI) designated matrix center conducting a wide range of interdisciplinary research in the areas of laboratory, clinical, and population sciences. The HDFCCC is led by the Director of the Center, who is assisted by the Deputy Director. The remainder of senior leadership is comprised of Associate Directors of: Basic Sciences/Translational Sciences, Clinical Sciences, Population Sciences, Shared Resources, Education, Community Engagement, Immunotherapy, Cancer Research at Zuckerberg San Francisco General, Developmental Therapeutics, Program Development, Cancer Research at San Francisco Veterans Administration Medical Center, and Administration.

Operational Definition of a Clinical Trial (NCI definition)

For purposes of the Data and Safety Monitoring Plan (DSMP), a clinical trial is operationally defined as a prospective study involving human subjects designed to answer specific questions about the health effects or impact of particular biomedical or behavioral interventions. Clinical trials may be described as therapeutic or non-therapeutic interventions and can include drugs, treatments, devices, as well as behavioral or nutritional strategies. Participants in these trials are patients with a diagnosis of cancer, or, in the case of primary prevention studies, at risk for cancer. Behavioral clinical trials include interventions whose goals are to increase behaviors (e.g., cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life (e.g., among cancer survivors) and reduce the negative effect of treatment. These non-therapeutic interventional trials may pertain to cancer prevention, screening and early detection, symptom management, and survivorship.

In the area of molecular or imaging diagnostics, a study is a clinical trial if it uses the information from the diagnostic test being evaluated in a manner that somehow affects medical decision-making for the participants beyond decision-making for the standard of care. In this way, a key goal of the trial is to collect diagnostic information that has an impact on some aspect of outcomes or clinical assessments. By contrast, studies which do not use information from the diagnostic test in any manner that can affect the outcome of participants, but whose objective is only the gathering of data on the characteristics of a new diagnostic approach, are minimal risk trials and are not covered by this DSMP. The exception to this would be if performing the diagnostic test itself imposes some risk on participants.

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

II. Responsibilities of the DSMC of the Helen Diller Family Comprehensive Cancer Center

The Data and Safety Monitoring Committee (DSMC)

The DSMC is responsible for monitoring and auditing interventional institutional trials for data validity, trial conduct, and serious adverse event (SAE) reporting. The risk assessment of the trial is determined by the phase of the trial, which in turn, designates the frequency of monitoring and auditing. Monitoring is performed in “real time” as participants are enrolled in the trial and involves the review of all participants; whereas auditing occurs at designated time points (i.e., biannually or yearly) and is the review of a determined percentage of the enrolled participants in the trial. The HDFCCC Director appoints the DSMC Chair. The DSMC Chair and the DSMC Director, together with the HDFCCC Cancer Center Clinical Research Oversight Committee (CCCROC) Chair appoints other members of the DSMC. The DSMC members may serve in the committee indefinitely, as there is not a term limit. The DSMC meets every six weeks.

Activities of the DSMC are overseen by the CCCROC. The DSMC Director provides reports to the HDFCCC Director and the HDFCCC CCCROC Chair detailing data and safety monitoring activities. Additionally, the minutes of each DSMC meeting are provided for review to the CCCROC Chair. When the DSMC identifies areas of concern, in addition to conferring with the CCCROC Chair, the DSMC Director notifies the Protocol Review and Monitoring Committee (PRMC), Clinical Research Support Office (CRSO), CCCROC, and the UCSF Institutional Review Board (IRB) as warranted. The DSMC Director oversees the Monitor/Auditor Supervisor, the Education and Training Manager and all auditors and monitors (indirectly through the DSMC Monitor/Auditor Supervisor) in the DSMC.

Members of the UCSF HDFCCC Data and Safety Monitoring Committee

Katie Kelley, MD	Chair and Gastrointestinal Oncology
Michelle Melisko, MD	Vice Chair and Breast Oncology
Jennie Taylor, MD	Vice Chair and Neurologic Oncology
Weiyun Ai, MD	Hematologic Oncology
Kristin Shimano, MD	Pediatric Oncology
Steve Braunstein, MD	Radiation Oncology
Rosanna Wustrack, MD	Surgical Oncology
Collin Blakely, MD	Thoracic Oncology
Vadim Koshkin, MD	Genitourinary Oncology
Joan Hilton, PhD	Biostatistics Core
Zoe Ngo, Pharm.D	Investigational Drug Service

Data and Safety Monitors/Education and Training Staff:

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

Phase I Trials

Phase I dose escalation trials are monitored prior to the requested dose escalation of the dosing cohort. All participants are monitored through the Dose Limiting Cohort until the Maximum Tolerated Dose (MTD) is determined. Once the MTD is determined, then the trial is audited on a semiannual basis with twenty percent of the participants enrolled in this expansion cohort through their first five cycles of treatment. Scheduled auditing of participant source documents is complete after all files have been reviewed for 2 cycles of treatment (20% of enrolled participants). For Phase I high risk therapeutic trials that are not dose finding, all participants are monitored on a quarterly basis (depending on accrual) through the first cycle of therapy. Monitoring of enrolled participants in the dose expansion portion of the trial will be complete after 20% of enrolled participants have been monitored through two cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), as well as audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

Vaccine/Gene Therapy Trials

Vaccine/gene therapy trials are monitored on a quarterly basis (depending on accrual) through the first month of therapy/treatment. Monitoring of all enrolled participants in these trials will be complete after all enrolled participants have been monitored through the first cycle of treatment. 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.

Phase II and III Trials

Phase II and III therapeutic trials are audited on a semiannual basis, with all data from twenty percent of the enrolled participants audited by the DSMC Monitor/Auditor through their first 5 cycles of 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 prior to submission of a safety lead-in report to the DSMC Chair for approval. After the safety lead-in request is granted by the DSMC Chair,

the trial is audited on a semiannual basis with twenty percent of the participants reviewed through the first 5 cycles of treatment. For all categories of phase II and III trials, auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

Non-Therapeutic Trials

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

Dose Escalations/Safety Lead-In Reviews

For dose escalation and safety lead-in requests, the DSMC Chair reviews the PI’s submitted request and DSMC monitoring report. For Conflict of Interests concerns (i.e., the DSMC Chair is the PI or a Sub-Investigator on the trial being reviewed or if the Chair is out of the office), then one of the DSMC Vice Chairs will review and approve these specific requests. Written authorization to proceed or a request for more information is issued within two business days of the request. The DSMC monitoring report and 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.

Regulatory audits

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

Monitoring Visit Reports (MVRs)

DSMC MVRs are reviewed at the DSMC meeting following the monitoring/auditing visit(s). The DSMC may request additional data or add recommendations. After the DSMC Chair approves the monitoring report, the report is then sent via e-mail to the PI and study team for follow-up. The study team will be provided a Monitoring Visit Report (MVR) within 20

business days after the completion of the review for follow-up action items. The responses to these follow-up action items will be due from the PI and the study team within 20 business days.

Serious Noncompliance Issues

If there are serious or continuing compliance issues or an increased risk to participant safety in a study trial or study program, the DSMC may mandate a temporary enrollment suspension for a trial or a study program until a robust corrective and preventative action plan (CAPA) is developed by the PI and study team or program. The DSMC will notify the CRSO Medical Director and the CRSO Director of the suspension so they may help develop, implement and ensure compliance with the CAPA. The PI and the study team will notify the 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 then notify the Industry Sponsor for Industry-Sponsored trials and the NCI Program Director for NCI-CTEP trials of the lifting of this suspension on trial activities.

III. Appendices

Appendix A.1 (Single Site) Phase I Dose Escalation

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

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

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

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

Scheduled auditing of participant source documents is complete after all files have been reviewed for five cycles of treatment (20% of participants). Monitoring of enrolled participants in the dose expansion phase of the trial will be complete after 20% of enrolled participants have

been monitored through two cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), as well as audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

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** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is 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 (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.

- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution

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

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

3.3 Dose Escalations

At the time of dose escalation, the PI submits a written and signed Dose Escalation Report to the DSMC Chair (or Vice Chair) and DSMC Director describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting Toxicities (DLTs) observed, in accordance with the protocol. The report will be reviewed by the DSMC Chair or Vice Chair and written authorization to proceed or a request for more information will be issued within two business days of the request. The report is then reviewed at the subsequent DSMC Committee meeting. In the event that the committee does not concur with the DSMC Chair's (or Vice Chair's) decision, study accrual is held while further investigation takes place.

3.4 Review of Adverse Event Rates

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

If at any time the PI voluntarily holds enrollment in the trial due to safety issues, the DSMC Chair (or Vice Chair) and DSMC Director must be notified within one business day via e-mail and the IRB must be notified as per IRB reporting regulations.

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Appendix A.2 (Single Site): High-Risk Vaccine or Gene-Therapy

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

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

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

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

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All clinically significant adverse events (AEs), whether or not considered expected or unexpected and whether or not considered associated with the investigational agent(s) or

study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

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

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

All adverse events entered into OnCore® will be reviewed on a weekly basis at the site committee meetings. The site committee will review and discuss the selected toxicity, the toxicity grade, and attribution assignment.

3.2 Serious Adverse Event Reporting

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

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

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

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

3.3 Review of Adverse Event Rates

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

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day via e-mail and the IRB must be notified as per their reporting regulations.

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Appendix A.3 (Single Site): Phase II or III Institutional Trial

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

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

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

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

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

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

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

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is 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 (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Permanent or significant disability/incapacity
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

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

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

3.3 Review of Adverse Event Rates

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

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

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

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

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

All institutional Phase II trials with a safety lead-in are designated with a high-risk assessment during the safety lead-in phase and a moderate risk assessment for the remainder of the trial. During the safety lead-in phase, the DSMC will audit all visits through the first cycle of treatment for all participants enrolled in this phase of the trial. After the completion of enrollment in the safety lead-in phase, the Principal Investigator will submit a report to the DSMC Chair outlining all AEs, SAEs, and DLTs (as defined in the protocol) with a request to proceed onto the next phase of the study. Within two business days of receipt, the DSMC Chair or designee will review the report and issue written authorization to proceed or a request for more information. The report is then reviewed at the subsequent DSMC meeting.

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

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

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

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

Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is 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 (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all 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 six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If an SAE involves death, and occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s), and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, then the event must be reported to the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

3.3 Review of Adverse Event Rates

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

If at any time the Principal Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and DSMC Director must be notified within one business day.

Data and Safety Monitoring Committee Contacts:

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Appendix A.5 (Single Site): Interventional Non-therapeutic Institutional Trial

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

1. Oversight and Monitoring Plan

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

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

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

2. Monitoring and Reporting Guidelines

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

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

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

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

review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

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

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered expected or unexpected and whether or not considered associated with the study intervention or procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

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

- **Definite** – The adverse event is clearly related to the study intervention or procedure.
- **Probable** – The adverse event is likely related to study intervention or procedure.
- **Possible** – The adverse event may be related to study intervention or procedure.
- **Unrelated** – the adverse event is 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 (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may

require medical or surgical intervention to prevent one of the outcomes listed above.

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

Serious adverse event reporting will be in accordance with all 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®, as well as submitted to the IRB. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

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

3.3 Review of Adverse Event Rates

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

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Appendix A.6 (Multicenter) Interventional Non-Therapeutic Multicenter Institutional Trial

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

1. Oversight and Monitoring Plan

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

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

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.

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for participant safety for all HDFCCC institutional clinical trials. For “greater than minimal risk” nontherapeutic trials, the assigned DSMC Senior Monitor/Auditor will audit three of the enrolled participants once per year, with a maximum of ten participant charts (across all sites) during the course of reviewing this trial until IRB closure. 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.

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

Auditing of all enrolled participants in these trials will be complete after 10 enrolled participants have been audited. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and

audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

2. **Multicenter communication**

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

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

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites as per the study-specific guidelines. The data (i.e., copies of source documents) from the participating sites will be downloaded into the CRA console of OnCore prior to the monitoring visits or the DSMC will be provided with access to the participating site's electronic medical record (EMR) system, in order for the DSMC to perform a remote audit of the participating site's compliance with the protocol.

3 **Review and Oversight Requirements**

3.1 **Adverse Event Monitoring**

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

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

- **Definite**– The adverse event is clearly related to the study intervention or procedure
- **Probable** – The adverse event is likely related to the study intervention or procedure.

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

Serious adverse event reporting will be in accordance with all 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®, as well as submitted to the IRB (per IRB guidelines). All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within one business day of becoming aware of the event. The SAEs are reviewed and monitored by the UCSF Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date of the submission of the SAE report to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within one business day from the participating site(s) and the Study Chair must then notify the DSMC Chair (or Vice Chair) and the DSMC Director within one business day of this notification.

3.3 Review of Adverse Event Rates

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

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Appendix A.7 (Multicenter): Phase 1 Dose Escalation

Data and Safety Monitoring Plan for a Multicenter Institutional Trial (Phase 1 Dose Escalation)

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

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

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

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

Multicenter communication

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. The UCSF Coordinating Center 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 or the DSMC will be provided with access to the participating site's electronic medical

record (EMR) access in order for the DSMC to perform remote monitoring of the participating site's compliance with the protocol and applicable FDA regulations

Dose Escalations

At the time of dose escalation, a written and signed Dose Escalation Report will be submitted to the DSMC Chair (or Vice Chair) and DSMC Director describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting Toxicities (DLTs) observed, in accordance with the protocol. The report will be reviewed by the DSMC Chair or Vice Chair and written authorization to proceed or a request for more information will be issued within two business days of the request. The report is then reviewed at the subsequent DSMC Committee meeting. In the event that the committee does not concur with the DSMC Chair's (or Vice Chair's) decision, study accrual is held while further investigation takes place.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

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

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

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is 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. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 1 business day of becoming aware of this event. 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 (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

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

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify

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

3.3 Review of Adverse Event Rates

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

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

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Appendix A.8 (Multicenter) High Risk Vaccine or Gene Therapy

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

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the trial and for monitoring its safety and progress at all participating sites. The Study Chair will conduct a review of data and participant safety at the weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

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

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

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

3. Review and Oversight Requirement

3.1 Adverse Event Monitoring

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

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

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is 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. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 1 business day of becoming aware of this event. 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 (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

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

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or

definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within one business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or Vice Chair and DSMC Director within one business day of this notification.

3.3 Review of Adverse Event Rates

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

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

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Appendix A.9 (Multicenter) Phase II or III Trial

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

1. Oversight and Monitoring Plan

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

- Semiannual 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.

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

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

Auditing of all enrolled participants in these trials will be complete after 20% of enrolled participants have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV)

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

Multicenter communication

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

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

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the remote monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and applicable FDA regulations.

3 Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), 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** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is 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 (i.e., results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious adverse event reporting will be in accordance with all 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®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within one business days of becoming aware

of the event. The SAEs are reviewed and audited by the UCSF Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or Vice Chair and the DSMC Director within 1 business day of this notification.

3.3 Review of Adverse Event Rates

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

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

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

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

1. Oversight and Monitoring Plan

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

- Review of all participant data in safety lead-in phase.
- Approval to enroll past safety lead-in phase by DSMC Chair or Vice Chair.
- Semiannual 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.

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

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

After DSMC authorization to enroll beyond the safety lead-in phase is granted, study data is audited by a DSMC Monitor/Auditor on a semiannual basis with a random selection of twenty percent of the participants (or at least three participants if the calculated value is less than three). The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the participants selected for review or until the selected participants discontinue study participation or the trial is closed with the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than 10 total participant charts during the course of auditing this trial. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the auditing visit is

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

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

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

Multicenter communication

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

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

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the remote monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and applicable FDA regulations.

3 Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the investigational agent(s) or study procedure, will be entered into OnCore®, UCSF's Clinical Trial Management System.

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

- **Definite** – The adverse event is clearly related to the investigational agent(s) or study procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or study procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or study procedure.
- **Unrelated** – the adverse event is 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 (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

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

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, then the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair (or Vice Chair) and the DSMC Director within 1 business day of this notification.

3.3 Review of Adverse Event Rates

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

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

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Appendix 11: 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 I dose-escalation therapeutic	Monitor all participants in real-time as prior to dose escalation through DLT period. Once DLT is determined, then audit 20% of participants through first five cycles of therapy.	Real time monitoring of AEs and SAE's weekly at site committees; DSMC monitors SAE every six weeks at DSMC Meetings
High	All Institutional therapeutic using gene therapy or vaccines, regardless of phase	Monitor all participants as enrolled through the first cycle of therapy.	Real time monitoring of AEs and SAEs weekly at site committees; DSMC monitors SAE every six weeks at DSMC Meetings
Moderate	Institutional Phase II therapeutic	Audit first five cycles of treatment in 20% of study participants on a semiannual basis	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors SAE every six 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 five cycles of treatment in 20% of study participant thereafter on a semiannual basis	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors SAE every six weeks at DSMC Meetings
Moderate	Institutional Phase III therapeutic	Audit first five cycles of treatment in 20% of participants on a semiannual basis	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors SAE every six weeks at DSMC Meetings
Low	Non-therapeutic trials with study procedures that are above minimal risk	Audit three participants enrolled in trial once per year, with a maximum of ten total participants reviewed for any given trial.	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors for SAEs every six weeks at DSMC Meetings

Risk assignment	Study type	Monitoring	Surveillance
Minimal Risk	Non-therapeutic trials with minimal risk procedures	Not responsible for auditing	Not responsible for auditing