UCSF Helen Diller Family Comprehensive Cancer Center

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

Revision #6 (27Sep2023)

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

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

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

All institutional 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 an assigned Data and Safety Auditor (DSA) 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, then the trial is audited on an annual basis. A total of twenty percent of the participants (maximum of 10 participants) enrolled in this expansion cohort will be reviewed through the first five cycles of treatment.

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

Scheduled auditing of participant source documents is complete after all files have been reviewed for five cycles of treatment for 20% of the enrolled participants in this cohort, with no more than 10 total participants reviewed during the course of auditing the expansion cohort. However, regulatory reviews of the trial, safety reviews (i.e., Serious

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

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

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

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

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

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

3.2 Serious Adverse Event Reporting

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

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or

- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

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

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

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

MedWatch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore, 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 eight 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) or research-related procedure, and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Principal Investigator or his/her designee must notify the DSMC Chair (or Vice Chair) and DSMC Director within one business day.

3.3 Dose Escalations

At the time of dose escalation, the PI submits a written and signed Dose Escalation Report to the DSMC Chair (or Vice Chair) and DSMC Director describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting Toxicities (DLTs) observed, in accordance with the protocol. The report will be reviewed by the DSMC Chair or Vice Chair and written authorization to proceed or a request for more information will be issued within two business days of the request. The report is then reviewed at the subsequent DSMC Committee meeting. In the event that the

committee does not concur with the DSMC Chair's (or Vice Chair's) decision, study accrual is held while further investigation takes place. Also, if there are AIRs that are past the due date for completions (i.e., post 8 week timeline or post 12-16 week timeline if extensions were granted), then the Dose Escalation review will be postponed until these action items are all addressed by the study team.

3.4 Review of Adverse Event Rates

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

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

Data and Safety Monitoring Committee Contacts:

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

Data and Safety Monitoring Plan for a High-Risk Non-Dose Finding Phase I Institutional Trial (Single Site)

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

All institutional non-dose finding therapeutic trials, are designated with a high-risk assessment. The data is monitored by an assigned Data and Safety Auditor (DSA) on a quarterly basis (depending on accrual) as participants are enrolled in the trial through the first month of study drug therapy. The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 20 business days after the monitoring visit is complete. This due date for the completion of the action items may be extended an additional 2 months for extenuating circumstances approved by the DSMC. The AIR report must be completed by the study team prior to the next review of this study. 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 monitoring of all enrolled participants in these trials has been completed, regulatory reviews, safety reviews (i.e., Serious Adverse Event (SAE) and Protocol Violation (PV) report reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

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

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

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

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

3.2 Serious Adverse Event Reporting

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

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it

does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with 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 eight 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 M.3 (Single Site): Phase II or III Institutional Trial

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

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

All institutional Phase II and III therapeutic trials are audited on an annual basis, with all data from 20% (maximum of 10 participants) of the enrolled participants audited by the assigned Data and Safety Auditor (DSA).

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

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 (or a total of 10 participants have been reviewed). However, regulatory reviews of the trial, safety

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

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

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

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

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

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

3.2 Serious Adverse Event Reporting

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

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or

- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

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

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

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

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

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 M.4 (Single Site): Phase II Trial with Safety Lead-In Phase
Data and Safety Monitoring Plan: Institutional (Single Site) Phase II Trial with Safety Lead-In Phase

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

All institutional Phase II trials with a safety lead-in are designated with a high-risk assessment during the safety lead-in phase and a moderate risk assessment for the remainder of the trial. During the safety lead-in phase, the DSMC will audit all visits through the first cycle of treatment for all participants enrolled in this phase of the trial. However, if there are AIRs that are past the due date for completions (i.e., post 8 week timeline or post 12-16 week timeline if extensions were granted, then the safety lead-in review will be postponed until these action items are all addressed by the study team.

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

After DSMC authorization to enroll beyond the safety lead-in phase is granted, study data is audited annually, with a random selection of 20% (with a maximum of 10 participants) of the participants reviewed. The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of

the action items may be extended an additional 2 months for extenuating circumstances approved by the DSMC. The AIR report must be completed by the study team prior to the next monitoring review of this study. 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 (or 10 total participants) have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

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

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

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

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

3.2 Serious Adverse Event Reporting

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

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

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

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

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

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore, All SAEs are reviewed and monitored by the DSMC on an ongoing basis and discussed at DSMC meetings, which take place every eight weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore.

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

3.3 Review of Adverse Event Rates

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

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

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Appendix M.5 (Single Site): 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 Data and Safety Auditor (DSA) 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 DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended an additional 2 months for extenuating circumstances approved by the DSMC. The AIR report must be completed

by the study team prior to the next auditing review of this study. 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) related to study procedures, whether considered expected or unexpected, will be entered into OnCore, UCSF's Clinical Trial Management System.

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

- **Definite** – clearly related to the study intervention or procedure.
- **Probable** – likely related to study intervention or procedure.
- **Possible** – may be related to study intervention or procedure.
- **Unrelated** – clearly not related to the study intervention or procedure.

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

3.2 Serious Adverse Event Reporting

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

- Death,
- Life-threatening adverse experience*,

- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

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

Serious adverse event reporting will be in accordance with all IRB regulations. For 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 eight 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 M.6 (Multicenter) Non-Therapeutic Multicenter Institutional Trial

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

1. Oversight and Monitoring Plan

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

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

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

For "greater than minimal risk" nontherapeutic trials, the assigned Data and Safety Auditor (DSA) will audit three of the enrolled participants once per year, with a maximum of ten participant charts (across all sites) during the course of reviewing this trial until IRB closure. If blood or tissue banking trials are determined to be "greater than minimal risk", then only Serious Adverse Events (SAEs) recorded in OnCore will be reviewed at each DSMC meeting for these trials. The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended an additional 2 months for extenuating circumstances approved by the DSMC. The AIR report must be completed by the study team prior to the next monitoring review of this study.

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

review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.
The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. Investigators will conduct a continuous review of data and participant safety at monthly site committee meetings where the status of each participant is discussed and documented in the site committee minutes.

2. Multicenter communication

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

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

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

3 Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 adverse events (AEs) related to study procedures, whether considered expected or unexpected, will be entered into OnCore, UCSF's Clinical Trial Management System.

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

of attribution or relationship to the study intervention or procedure. Attribution categories are:

- **Definite**– clearly related to the study intervention or procedure.
- **Probable** –likely related to the study intervention or procedure.
- **Possible** – may be related to the study intervention or procedure.
- **Unrelated** – clearly not related to the study intervention or procedure.

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

3.2 Serious Adverse Event Reporting

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

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

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

Serious adverse event reporting will be in accordance with all IRB regulations. For 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 eight weeks. The date of the submission of the SAE report to all required reporting agencies will be documented in OnCore.

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

3.3 Review of Adverse Event Rates

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

3.4 Data and Safety Monitoring Board (DSMB) Reports

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

Data and Safety Monitoring Committee Contacts:

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

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

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

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

All multicenter phase I dose escalation trials are monitored prior to the requested dose escalation of the dosing cohort. All participants are monitored through the Dose Limiting Cohort until the Maximum Tolerated Dose (MTD) is determined. Once the MTD is determined, then the trial is audited on an annual basis with twenty percent of the participants enrolled in this expansion cohort that are audited through their first five cycles of treatment. Scheduled auditing of participant source documents is complete after all files have been reviewed for five cycles of treatment. 20% of the enrolled participants in the expansion cohort, with no more than 10 total participants reviewed during the course of auditing this expansion cohort, will be reviewed. 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 month of therapy.

The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from the Action Item Report (AIR) report within 8 weeks. The due date for the completion of the action items may be extended an additional 2 months for extenuating circumstances approved by the DSMC. The AIR report must be completed by the study team prior to the next monitoring review of this study. 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 one cycle of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), as well as audit/inspection preparation (as applicable) will continue until 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. However, if there are AIRs that are past the due date for completions (i.e., post 8 week timeline or post 12-16 week timeline if extensions were granted), then the Dose Escalation review will be postponed until these action items are all addressed by the study team.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

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

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

of attribution or relationship to investigational agent or study procedure. Attribution categories are:

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

All adverse events entered into OnCore will be reviewed on a weekly basis at the UCSF Coordinating Center's Site Committee meetings. The UCSF Site Committee will review and discuss the selected toxicity, grade, and the attribution assignment for the adverse events that occurred at both the UCSF Coordinating Center and the participating sites.

3.2 Serious Adverse Event Reporting

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

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

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

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

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event
Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore, 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 all, whichever is sooner. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every eight weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore.

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

3.3 Review of Adverse Event Rates

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

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

3.4 Data and Safety Monitoring Board (DSMB) Reports

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

Data and Safety Monitoring Committee Contacts:

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Appendix M.8 (Multicenter) Non-Dose Finding Phase I Multicenter Trial

Data Safety Monitoring Plan for Non-Dose Finding Phase I Multicenter Trial

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

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

All **non-dose finding high risk Phase I** therapeutic trials, regardless of the study phase, are designated with a high-risk assessment. The data is monitored by a Data and Safety Auditor (DSA) on a quarterly basis as participants are enrolled in the trial through the first month of study drug therapy. All institutional non-dose finding therapeutic trials, are designated with a high-risk assessment. The data is monitored by an assigned Data and Safety Auditor (DSA) on a quarterly basis (depending on accrual) as participants are enrolled in the trial through the first month of study drug therapy. The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 20 business days after the monitoring visit is complete. This due date for the completion of the action items may be extended an additional 2 months for extenuating circumstances approved by the DSMC. The AIR report must be completed by the study team prior to the next review of this study. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will

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

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

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

Multicenter communication

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

- Enrollment information.
- Adverse events
- Protocol Violations.
- Other issues affecting the conduct of the study.

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

3. Review and Oversight Requirement

3.1 Adverse Event Monitoring

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

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

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

All adverse events entered into OnCore® will be reviewed on a weekly basis at the UCSF Coordinating Center's Site Committee meetings. The UCSF Site Committee will review and discuss the selected toxicity, grade, and the attribution assignment for the adverse events that occurred at both the UCSF Coordinating Center and the participating sites.

3.2 Serious Adverse Event Reporting

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

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

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

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.
UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

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 eight weeks.

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

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

3.3 Review of Adverse Event Rates

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

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

3.4 Data and Safety Monitoring Board (DSMB) Reports

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

Data and Safety Monitoring Committee Contacts:

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

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

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

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

All institutional Phase II or III therapeutic trials are designated with a moderate risk assessment. The data is audited by a Data and Safety Auditor (DSA) on an annual basis with a random selection of 20% of the participants (with a maximum of 10 participants reviewed). The DSA 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. The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 20 business days after the monitoring visit is complete. This due date for the completion of the action items may be extended an additional 2 months for extenuating circumstances approved by the DSMC. The AIR report must be completed by the study team prior to the next review of this study. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

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

The participating site's source documents are audited remotely via either review of redacted source documents downloaded by the site into the CRA console of OnCore and/or via access to the site's electronic medical records. The DSA will audit up to three participant charts at each participating site during the course of auditing this trial.

Multicenter communication

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

- Enrollment information.
- Adverse events.
- Protocol Violations.
- Other issues affecting the conduct of the study.

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

3 Review and Oversight Requirements

3.1 Adverse Event Monitoring

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

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

of attribution or relationship to the investigational agent(s) or study procedure. Attribution categories are:

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

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

3.2 Serious Adverse Event Reporting

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

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

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

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

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

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore, 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 eight weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore.

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

3.3 Review of Adverse Event Rates

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

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

3.4 Data and Safety Monitoring Board (DSMB) Reports

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

Data and Safety Monitoring Committee Contacts:

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Appendix M.10 (Multicenter) Phase II or III Trial with Safety Lead-In Phase
Data and Safety Monitoring Plan: Multicenter Phase 2 or 3 Trial with Safety Lead-In

1. Oversight and Monitoring Plan

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

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

2. Monitoring and Reporting Guidelines

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

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

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

After the completion of enrollment in the safety lead-in phase, the Study Chair will submit a report to the DSMC Chair outlining all AEs, SAEs, and DLTs (as defined in the protocol) with a request to proceed onto the next phase of the trial. Within two business days of receipt, the DSMC Chair or designee will review the report and issue written authorization to proceed or a request for more information. The report is then reviewed at the subsequent DSMC meeting. However, if there are AIRs that are past the due date for completions (i.e., post 8 week timeline or post 12-16 week timeline if

extensions were granted), then the safety lead-in review will be postponed until these action items are all addressed by the study team.

After DSMC authorization to enroll beyond the safety lead-in phase is granted, study data is audited by a DSMC Monitor/Auditor on an annual basis with a random selection of 20% of the participants (no more than 10 participants). 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. The DSA will send both a Monitoring Visit Report (MVR) and an Action Item Report (AIR) to the study team within 20 business days after the monitoring visit is complete. This due date for the completion of the action items may be extended an additional 2 months for extenuating circumstances approved by the DSMC. The AIR report must be completed by the study team prior to the next review of this study. 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 (or a total of 10 participants) have been audited through five cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), and audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

Multicenter communication

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

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

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

3 Review and Oversight Requirements

3.1 Adverse Event Monitoring

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

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

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

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

3.2 Serious Adverse Event Reporting

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

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- Life-threatening adverse experience*,
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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 eight weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore.

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

3.3 Review of Adverse Event Rates

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

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

3.4 Data and Safety Monitoring Board (DSMB) Reports

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

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Appendix N: Risk Assessment for Institutional Studies

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

Risk assignment	Study type	Monitoring	Surveillance
High	Institutional Phase 1 dose-escalation therapeutic	Monitor all participants in real-time as prior to dose escalation through DLT period. Once DLT is determined, then audit 20% of participants (maximum of 10 participants) through first five cycles of therapy.	Real time monitoring of AEs and SAEs weekly at site committees; DSMC monitors SAEs every eight weeks at DSMC Meetings
High	non-dose finding Phase I Institutional therapeutic	Monitor all participants on a quarterly basis as enrolled through the first cycle of therapy.	Real time monitoring of AEs and SAEs weekly at site committees; DSMC monitors SAEs every eight weeks at DSMC Meetings
Moderate	Institutional Phase II therapeutic	Audit first five cycles of treatment in 20% of study participants (maximum of 10 participants) on an annual basis	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors SAEs every eight weeks at DSMC Meetings
Moderate	Institutional Phase II therapeutic with Safety Lead-In	Monitor all patients in the safety lead-in cohort, then audit first five cycles of treatment in 20% of study participant (maximum of 10 participants) thereafter on an annual basis	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors SAEs every eight weeks at DSMC Meetings
Moderate	Institutional Phase III therapeutic	Audit first five cycles of treatment in 20% of participants on an annual basis with a	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors for SAEs every eight weeks at DSMC Meetings

Risk assignment	Study type	Monitoring	Surveillance
		maximum of ten total participants reviewed	
Low	Non-therapeutic trials with research specific study procedures that are deemed above minimal risk (i.e., novel tracers for radiology trials)	Audit three participants enrolled in trial once per year, with a maximum of ten total participants reviewed.	Real time monitoring of AEs and SAEs monthly at site committees; DSMC monitors for SAEs every eight weeks at DSMC Meetings
Minimal Risk	Non-therapeutic trials with minimal risk study procedures	Not responsible for auditing	Real time monitoring of SAEs monthly at site committees; DSMC monitors for SAEs every eight weeks at DSMC Meetings