

**University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center**

**Guideline for the Data and Safety Monitoring of Phase 1 Institutional Single Site
and Multicenter Trials by the HDFCCC DSMC**

Process for the monitoring of Phase I and high-risk institutional trials by the HDFCCC DSMC

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Purpose

The purpose of this guideline is to define the process by which institutional therapeutic Phase 1 single site and multicenter/consortium oncology clinical trials at the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) are monitored by the HDFCCC Data and Safety Monitoring Committee (DSMC) Monitors/Auditors.

Scope

This guideline is applicable to all HDFCCC institutional therapeutic Phase 1 trials under the purview of the HDFCCC DSMC. The guideline describes the monitoring/auditing requirements for HDFCCC DSMC Monitors and Auditors and requirements for staff and faculty conducting Phase 1 institutional clinical research at the HDFCCC.

Definitions

Phase I: studies which test the safety, side effects, best dose, and timing of a new treatment. It may also test the best way to give a new treatment (for example, by mouth, infusion into a vein, or injection) and how the treatment affects the body. The dose is usually increased a little at a time in order to find the highest dose [Maximum Tolerated Dose (MTD)] that does not cause harmful side effects in order to determine the Recommended Phase 2 Dose (RP2D).

Dose Limiting Toxicity (DLT): a significant side effect of an experimental treatment that is serious enough to prevent an increase in dose or level of that treatment in a dose-finding trial.

Institutional: defined in this guideline as to when UCSF is the Sponsor of an Investigator-initiated trial.

Maximum Tolerated Dose: the highest dose of a drug or treatment that does not cause unacceptable side effects. The maximum tolerated dose is determined in Phase I trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found.

Monitoring: the act of overseeing the conduct of a clinical trial, that is, ensuring that the trial is conducted according to protocol, GCP, SOP and regulatory requirements.

Consortium: an integrative group of cancer centers that perform clinical trials of experimental therapies.

Source Documents: All information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate.

Case Report Form (CRF) is a printed, optical, or electronic document designed to record all protocol-required information on each participant in a clinical research study. The CRF facilitates complete and standardized data collection that promotes efficient processing,

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analysis, and reporting of information, as well as exchange of data across sites and to the Sponsor/Principal Investigator/Data Coordinating Center.

Background

The HDFCCC DSMC Monitors/Auditors are responsible for monitoring participant safety and data integrity for institutional therapeutic Phase I trials conducted at the HDFCCC as per National Cancer Institute (NCI) requirements and as per risk assessment in the NCI approved [HDFCCC DSMP](#).

Procedures

Monitoring Overview

All Institutional Phase I therapeutic dose escalation trials are designated with a high-risk assessment; therefore, the source documents for all enrolled participants in each dosing cohort are monitored by a DSMC Monitor/Auditor prior to approval of the dosing cohort. This includes a review of all study information through the first post-Dose Limiting Toxicity period (DLT period) visit of the trial up until the maximum tolerated dose (MTD) is determined. Once the MTD is determined, the trial will then be audited annually in the cohort expansion phase, with 20 percent of the enrolled study participants audited for the first five cycles of treatment, with a maximum of 10 additional charts reviewed. DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the monitoring visit is complete. The PI and the study team must resolve all action items from this report within 20 business days after receiving this monitoring visit report. An abbreviated regulatory review will occur at each participant monitoring review; however, a full regulatory review will occur on a biennial basis by the DSMC for regulatory compliance.

Site Initiation Visit

For multicenter or consortium trials, a HDFCCC study team member will invite the assigned DSMC Monitor/Auditor to the scheduled Site Initiation Visit (SIV) with the participating sites. The DSMC Monitor/Auditor will attend to ensure that the monitoring process is clearly communicated to all parties involved.

Process for Scheduling Remote and On-Site Monitoring Visits

The DSMC Monitor/Auditor Supervisor will assign a DSMC Senior Monitor/Auditor for each Investigator Initiated Trial (IIT) at the time of Protocol Review and Monitoring Committee (PRMC) approval. The assigned DSMC Senior Monitor/Auditor will receive notification from an OnCore report when the Phase I trial is open to accrual.

The assigned DSMC Monitor/Auditor and the assigned Clinical Research Coordinator will communicate regarding trial accrual and participant monitoring in each treatment cohort. For therapeutic trials only, all participant study data to be reviewed by the HDFCCC must be entered in OnCore or other approved Electronic Data Capture (EDC) system by the study team prior to the DSMC monitoring visit. The DSMC Monitor/Auditor will not monitor data entry for non-therapeutic trials unless the PI has developed eCRFs in OnCore or other approved EDC system. The DSMC will only be performing remote reviews only, with the exception of urgent

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requests (i.e., audit or inspection prep) for which the DSMC may provide on-site review on a case by case basis.

The DSMC Monitor/Auditor will schedule the monitoring visit with the UCSF study team or the participating site at least 6 weeks prior to the monitoring visit, where feasible. The DSMC Monitor/Auditor will provide an Outlook invite, as well as the information regarding the type of visit and the exact files to review via a confirmation letter, completed from the [Monitoring E-mail Template](#). The UCSF Box [e-chart template](#) will be included, in which the participant source documents can be organized by the study teams in order to ensure efficient review by the DSMC. Additionally, a [Naming Convention for Uploading Source Documents](#) link will be included as well to provide guidance for the naming of the source document files. The participant source documents must be provided in an organized format (as per the organizational structure of the UCSF Box e-chart template or, if provided in a pdf, the files must be provided in an organized structure with bookmarks for each file/report) that is approved for the DSMC Monitor/Auditor to review for the auditing visit. If the source documents aren't provided in an organized manner, then the participant monitoring visit will need to be postponed until the source documents are organized for this review.

At each participant monitoring visit, a limited regulatory review will occur (i.e., review of the approved protocol and (ICF) versions, along with the Delegation of Authority Log, Financial Disclosure Form (FDF), and the FDA 1572 form). The formal regulatory audits will include a review of all regulatory documents for the trial on a biennial basis. As noted above, the regulatory documents must be provided in an organized manner or the regulatory monitoring visit will be required to be postponed until the source documents are provided in an organized fashion.

Rescheduling Monitoring Visits

Once scheduled by the DSMC Auditor/Monitor, monitoring visits may only be rescheduled for extenuating circumstances. If the visits are rescheduled more than one time, the DSMC Chair (or Vice Chair) and DSMC Director will be notified. The PI and the study team may be required to meet with the DSMC, as well as the Director of the CRSO, in order to discuss adherence to the monitoring plan.

Monitoring Visits

Effective 19Nov2021, the HDFCCC DSMC will be reviewing electronic source documents (i.e., electronic participant charts and electronic regulatory documents (Complion, SharePoint, regulatory documents from the study team central files, etc.)) for monitoring visits; however, the DSMC may be reviewing legacy "paper" source documents and regulatory documents on-site at UCSF for audit and inspection preparation (i.e., CTEP, FDA, Sponsor, etc.), as applicable.

The DSMC Monitor/Auditor and the assigned CRC or study team member will sign a DSMC Monitoring Log for each day the trial is reviewed. The source documents are reviewed to ensure that there is adherence to the protocol, and to identify any safety issues with the conduct of the study. The monitoring visit includes the review of the following source documents:

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- Informed consent forms, Health Information Portability Accountability Act (HIPAA) authorization, and Experimental Participants Bill of Rights (California sites only) documents properly obtained.
- All required screening tests and procedures are obtained and reviewed by the PI or qualified investigator on DOA prior to the start of treatment.
- Supporting documentation to show that all eligibility criteria were met.
- Adherence to treatment plan is documented, including Investigational Product (IP) orders, drug doses and dose reductions and/or treatment holds, if indicated.
- Accuracy, adequacy, completeness, and timeliness of data collection and submission.
- Appropriate and timely recording of adverse events (AEs) and reporting serious adverse events (SAEs) to the IRB, Sponsor, and FDA (if applicable).
- Review of possible dose limiting toxicities (DLTs).
- Adherence to participant follow-up requirements.
- Verifying all data in the electronic case report forms using the source documents.

For the review of a participating site's source documents in a multicenter or consortium trial, the DSMC Monitor/Auditor will either review the source documents uploaded in the applicable electronic repository noted in the protocol. As noted above, these source documents must be provided in an organized manner for the DSMC Monitor/Auditor to review. If the source documents are not provided in an organized manner and/or data entry in OnCore or other approved EDC system is incomplete (for therapeutic trials only), then the monitoring visit will need to be rescheduled until the source documents are organized for this review and data entry is complete.

After completion of the monitoring visit, the assigned DSMC Monitor/Auditor will meet either remotely or in person with the CRC, regulatory contact (if a regulatory review was performed), and the PI (if there are significant findings) in order to review the findings and discuss the required follow-up action items.

For Dose Escalation approval requests, the HDFCCC PI (or qualified Sub-Investigator listed on the Delegation of Authority Form) and study team representative must complete the [DSMC Dose Escalation Report](#) (See DSMC link on this HDFCCC webpage). The DSMC Monitor/Auditor will review the report for completeness and accuracy, and will submit the completed Dose Escalation Report, signed and dated by the PI, to the DSMC Chair (or Vice Chair) and Director requesting approval for dose escalation prior to enrollment of the next cohort as per protocol. The DSMC Chair (or Vice Chair) will grant approval of this dose escalation request within 48 hours of receipt from the DSMC Auditor/Monitor if there aren't any significant safety issues (i.e., undocumented DLTs, SAEs, protocol violations, etc.) in the patient dosing cohort that was monitored.

Post-Monitoring Visit

Following the completion of the monitoring visit, the DSMC Monitor/Auditor will complete the Monitoring Visit Report (MVR) and the DSMC Monitoring Report Action Items Worksheet, which describes the findings of this monitoring visit. The study is given an overall evaluation by the DSMC Senior Monitor/Auditor, with approval by the DSMC Supervisor, DSMC Director, and DSMC Chair (or Vice Chair) of one of the following evaluations:

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- Acceptable with no follow-up items to be completed.
- Acceptable with follow-up items to be completed.
- Significant findings, with follow-up CAPA required to be submitted to the DSMC within 10 business days, along with notifying the PRMC and IRB.
- Unsatisfactory, halt enrollment of new subjects, corrective action plan required within 10 days to the DSMC. The DSMC Chair or delegate will notify the PRMC and the IRB accordingly.

The Monitoring Visit Report (MVR) is then electronically signed by the DSMC Monitor/Auditor, DSMC Supervisor, DSMC Director, and the DSMC Chair or Vice Chair and then is sent (along with the DSMC Monitoring Report Action Item Worksheet) to the HDFCCC PI, CRC, Clinical Research Manager (CRM) regulatory contact (for regulatory reviews only), assigned HDFCCC Associate Director (AD) (as per the [HDFCCC Point of Contact Listing](#)), and the participating site's Investigator and study team representative within 20 business days of completion of the monitoring visit. The signed MVR is uploaded into the PC console under "documents" in OnCore and this monitoring information will be updated in the DSMC tab under the PC console. Additionally, the report is also filed in the internal DSMC electronic files. The signed copy of this MVR is provided to the DSMC Director for inclusion in the DSMC Meeting Binder.

The PI and the study team will have 20 business days from the receipt of the MVR to complete the action items on the DSMC Monitoring Report Action Items Worksheet and provide to the assigned DSMC Monitor/Auditor once completed. The DSMC Monitor/Auditor will then electronically sign this DSMC Monitoring Report Action Items Worksheet to confirm completion of all action items. The assigned DSMC Monitor/Auditor will verify that the queried eCRFs in the Queried Forms section of OnCore have been adequately addressed by the study team and will then mark each queried form as "validated". If follow-up action items from the MVR are not resolved within the 20-day timeframe for response, the assigned DSMC Senior Monitor/Auditor will let the PI, assigned CRC, and study team or participating site staff member know that future dose escalations may not be granted by the DSMC until all follow-up action items are resolved.

References

- [Guidance for Industry Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring. Food and Drug Administration.](#)
- [Helen Diller Family Comprehensive Cancer Center Data and Safety Monitoring Plan \(DSMP\).](#)
- [21 CFR 312.50.](#)
- [21 CFR 812.40.](#)

Appendices

None