

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

**Guideline for Data and Safety Auditing of Single Site and Multicenter Phase 2 and
3 Trials by the HDFCCC DSMC**

Process for the auditing of moderate and low risk Phase 2 and 3 institutional trials by the
HDFCCC DSMC

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Purpose

This guideline defines the process by which therapeutic and non-therapeutic Institutional single site and multicenter/consortium Phase 2 and 3 oncology clinical trials at the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) are audited by the HDFCCC Data and Safety Monitoring Committee (DSMC) Monitors/Auditors.

Scope

The scope of this guideline is to describe the auditing process of how the HDFCCC DSMC Monitors and Auditors review the HDFCCC institutional non-therapeutic and therapeutic Phase 2 and 3 trials and how it applies to all staff and faculty conducting clinical research at the HDFCCC.

Definitions

Phase 2: once the Recommended Phase 2 Dose (RP2D) from the Phase I trial has been determined, then this type of trial determines the biological activity, safety, and efficacy of this dose in a larger group of study participants.

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

Safety Lead-in Cohort: short pilot or run-in period in order to explore a limited number of dose levels or to evaluate the anticipated recommended RP2D directly prior to enrolling patients in the main portion of the Phase 2 trial.

Audit: a systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported, according to the protocol and sponsor's standard operating procedures (SOPs) and the applicable 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, analysis, and reporting of information, as well as exchange of data across sites and to the Sponsor/Principal Investigator/Data Coordinating Center.

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Background

The HDFCCC DSMC Monitors/Auditors are responsible for auditing all therapeutic and non-therapeutic Institutional Phase 2 and 3 clinical trials for data validity, trial conduct, and participant safety as per the risk assessment algorithm in the [HDFCCC Data and Safety Monitoring Plan \(DSMP\)](#).

The risk assessment of the study is determined by both the risk and the phase of the trial, which in turn, designates the frequency of auditing for each trial. In general, for single site and multicenter/consortium Phase 2 and 3 trials, twenty percent of the enrolled study participants are audited on an annual basis starting within one month of the initiation of enrollment in the trial.

The DSMC Monitor/Auditor Supervisor will assign a DSMC Monitor/Auditor for each Investigator Initiated Trial (IIT) at the time of Protocol Review and Monitoring Committee (PRMC) approval of the trial, as per notification from an automatic OnCore report. The assigned DSMC Monitor/Auditor will receive notification from OnCore when the Phase 2 or 3 trial has started enrollment. The assigned DSMC Monitor/Auditor and the assigned Clinical Research Coordinator will communicate regarding trial accrual and scheduling participant auditing.

The DSMC Monitor/Auditor will audit a maximum of five cycles of treatment in the twenty percent of the participants selected for the review until either the selected participants for the audits have completed the trial, or the trial is closed by the IRB. Additionally, the assigned DSMC Monitor/Auditor will review no more than 10 total participant charts, including at least one participant chart from each participating site, during the time interval of “open to accrual” to “IRB closure”, unless there are more than 10 sites participating over the course of the study, in order to ensure that at least 1 participant chart per site is reviewed.

For “greater than minimal risk” Phase 2 or 3 institutional nontherapeutic trials, the assigned DSMC Monitor/Auditor will audit three of the enrolled participants on an annual basis, with a maximum of 10 participant charts audited until the trial is closed by the IRB.

A limited regulatory review will occur at each auditing visit (i.e., review of the approved protocol and ICF versions, along with the Delegation of Authority Log, Financial Disclosure Form (FDF), and the FDA 1572 form); however, a complete regulatory review will occur on a biennial basis by the DSMC for regulatory compliance.

Procedures

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 auditing process is clearly communicated to all parties involved.

Process for Scheduling Remote and On-Site Auditing Visits

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The assigned DSMC Monitor/Auditor will be in communication with the assigned CRC and review trial enrollment in OnCore. For therapeutic trials, all participant study data to be reviewed at the HDFCCC and participating site(s) must be completed in OnCore or other approved Electronic Data Capture (EDC) system by the study team prior to the DSMC auditing visit. The DSMC Monitor/Auditor will not monitor data entry for non-therapeutic trials, unless the Investigator has developed eCRFs in OnCore or other approved EDC system. The DSMC will be performing remote reviews, with the exception of urgent requests (i.e., audit or inspection prep) in which we may provide on-site review.

The DSMC Monitor/Auditor will schedule the auditing visit with the UCSF PI or the participating site's PI at least 6 weeks prior to the anticipated auditing visit date, as feasible. The DSMC Monitor/Auditor will provide an Outlook invite, as well as 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 to ensure efficient review. 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 (i.e., 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 organized in approved organized fashion and/or data entry in OnCore or other approved EDC system is incomplete, then the auditing visit will be postponed until the source documents are organized for this review and data entry is complete.

At each participant monitoring visit, a limited regulatory review will occur (i.e., review of the approved protocol and informed consent (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 auditing visit will need to be postponed until the documents are provided in an organized fashion.

Rescheduling Auditing Visits

Once scheduled by the DSMC Auditor/Monitor, auditing 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.

Auditing Visits

Effective 19Nov2021, the HDFCCC DSMC will be reviewing electronic source documents (i.e., electronic participant charts enrolled after 01Mar2020 and electronic regulatory documents (Complion, SharePoint, regulatory documents from the study team central files, etc.)) for auditing 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.

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The DSMC Monitor/Auditor and the 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:

- Informed consent forms, Health Information and Portability (HIPAA), and Experimental Participants Bill of Rights (California sites only) documents.
- All required screening tests and procedures are obtained and reviewed by the PI 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).
- Adherence to participant follow-up requirements.
- Verifying all data in the electronic case report forms using the source documents.

After completion of the auditing visit, the assigned DSMC Monitor/Auditor will meet either remotely or in person with the HDFCCC 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 follow-up action items.

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.

For Safety Lead-in Cohorts, the HDFCCC PI and study team representative must complete the [DSMC Study Safety Lead-In Report](#) (See DSMC Link on the HDFCCC website). The DSMC Monitor/Auditor will review the report for completeness and accuracy, and will submit the completed DSMC Study Safety Lead-In Report, signed and dated by the PI, to the DSMC Chair (or Vice Chair) and Director requesting approval from the DSMC prior to further enrollment in the trial as per protocol. The DSMC Chair (or Vice Chair) will grant approval of this request within 48 hours from receipt from the DSMC Auditor/Monitor if there aren't any significant safety issues (i.e., SAEs, protocol violations, etc.) in the participant cohort that was audited.

Post-auditing Visit

Following the completion of the auditing visit, the DSMC Monitor/Auditor will complete the Monitoring Visit Report (MVR) and the DSMC Monitoring Report Action Item Worksheet, which describes the findings from this auditing visit. The study is given an overall evaluation by the

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DSMC Senior Monitor/Auditor, with approval by the DSMC Supervisor, DSMC Director, and DSMC Chair (or Vice Chair) of one of the following evaluations:

- 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 is 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. Additionally, the signed Monitoring Visit Report (MVR) is uploaded into the PC console under "documents" in OnCore and the DSMC tab in the PC console is updated with this auditing information as well. 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", which will then be automatically moved into the Amended Forms section of OnCore. If follow-up action items from the MVR are not resolved within the 20-day timeframe for response, the assigned DSMC Monitor/Auditor will let the PI, assigned CRC, and study team or participating site staff member know that future accrual may be held 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