University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
Policy and Procedure

Policy for Data and Safety Auditing of Phase 2 or 3 Single Site and Multicenter Trials

Purpose

This policy defines the process by which interventional therapeutic Phase 2 Single and Multicenter Site oncology clinical trials at the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) are audited by the Data and Safety Monitoring Committee (DSMC) Monitors/Auditors.

Scope

This monitoring policy applies to all staff and faculty conducting clinical research at the HDFCCC.

Background

The HDFCCC DSMC Monitors/Auditors are responsible for providing monitoring/auditing for all interventional therapeutic and non-therapeutic 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 monitoring/auditing for each trial. In general, the HDFCCC participant "shadow charts" for single site and multicenter site Phase 2 trials are audited on a semiannual basis, dependent upon accrual, beginning within one month of the initiation of enrollment in the trial. The participating site's source documents are audited remotely via either review of redacted source documents downloaded by the site into the PC console of OnCore or via access to the site's electronic medical records.

For "greater than minimal risk" Phase 2 or 3 nontherapeutic trials, 20% of the enrolled study participants are audited once per year. If blood or tissue banking trials are determined to be "greater than minimal risk", then only Serious Adverse Events (SAEs) occurring in these trials are reviewed at future DSMC meetings. A limited regulatory review occurs at each scheduled auditing visit to review items such as the approved protocol and ICF versions, along with the Delegation of Authority Form and the FDA 1572 forms, while a complete regulatory audit reviewing all regulatory documents is performed on a biennial basis.

Procedures

The DSMC Supervisor or Director assigns a DSMC Monitor/Auditor for each Investigator Initiated Trial (IIT) at the time of Protocol Review Committee (PRC) approval. The assigned Clinical Research Coordinator (CRC), Clinical Research Manager (CRM), or Protocol Project Manager (PPM) will notify the assigned DSMC Monitor/Auditor when the Phase 2 or 3 trial has started enrollment. Additionally, the CRC or CRM will notify the assigned DSMC Monitor/Auditor when the Site Initiation Visit (SIV) with the participating site(s) is scheduled so

the DSMC Monitor/Auditor can attend to ensure that the auditing process is clearly communicated to the participating site staff. The assigned DSMC Monitor/Auditor will review trial enrollment in OnCore in order to schedule an auditing visit with the study team.
All participant study data at the HDFCCC and participating site(s) must be entered in OnCore or an approved Electronic Data Capture (EDC) system by the study team prior to the DSMC Monitor/Auditor scheduling an auditing visit with the study team at any site. For safety lead-in cohorts, the assigned CRC will notify the assigned DSMC Monitor/Auditor in order to ensure scheduling of an auditing visit for all study participants in the safety lead-in cohort prior to safety review request by the Principal Investigator (PI) and study team to the DSMC Chair and DSMC Director.

The assigned DSMC Monitor/Auditor will notify the HDFCCC PI, assigned CRC, and CRM and the participating site Investigator and study team members in order to schedule a subject auditing visit. The HDFCCC PPM or participating site regulatory contact is notified for regulatory audits. Once the monitoring visit date is scheduled, the HDFCCC PI and study team members and the participating site Investigator and study team members are notified regarding the details of this visit, including the number of participants to be audited. A limited regulatory review in iRIS occurs at each scheduled auditing visit to review items such as the approved protocol and ICF versions, along with the Delegation of Authority Form and the FDA 1572 forms, while a complete regulatory audit reviewing all regulatory documents is performed on a biennial basis. In general, the HDFCCC participant "shadow charts" for single site and multicenter site Phase 2 trials are audited on a semiannual basis, dependent upon accrual, beginning within one month of the initiation of enrollment in the trial. The DSMC Monitor/Auditor will audit a maximum of 5 cycles of treatment in the 20% of the participants selected for the review until either these selected participants 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 during the time interval of open to enrollment by the IRB until IRB closure. The participating site's source documents are audited remotely via either review of redacted source documents downloaded by the site into the PC console of OnCore or via access to the site's electronic medical records. The DSMC Monitor/Auditor will audit no more than 3 participant charts at each participating site during the course of auditing this trial.

For "greater than minimal risk" Phase 2 or 3 nontherapeutic trials, the assigned DSMC Senior Monitor/Auditor will audit 3 of the enrolled participants once per year, with a maximum of 10 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) for these trials at future DSMC meetings.

The assigned DSMC Monitor/Auditor will remind the assigned HDFCCC CRC and the participating site CRC to ensure that all shadow charts or redacted source documents are prepared and that all information entered in OnCore, or in the trial-specific electronic data capture (EDC) system is complete for all participants to be audited prior to this scheduled visit. For the review at UCSF, the DSMC Monitor/Auditor will either review the chart on site, or in cases where space to work is not available, will bring the shadow charts back to their office. The "shadow" charts will be kept in a locked cabinet at the end of each day. If it is necessary for the charts to be kept over the weekend, the assigned CRC will be notified by the DSMC Monitor/Auditor for approval. For the review of the participating site's source documents, the

DSMC Monitor/Auditor will either review the redacted source documents downloaded to the PC console of OnCore or will review the source documents from the site's EMR. The DSMC Monitor/Auditor will audit the shadow charts as the original source documents and source document verify data entry in the electronic case report forms. The source documents are reviewed to ensure that there is adherence to the protocol and to identify if there are safety issues with the conduct of the study. The auditing visit includes the review of the following source document information:

- Informed consent forms, HIPAA, and, Bill of Rights documents properly obtained.
- All required pre-study tests and procedures are obtained and reviewed by the PI prior to the start of treatment.
- All eligibility criteria reviewed to ensure that the study patient is qualified for the trial.
- Adherence to treatment plan is documented, including Investigational Product (IP) orders, drug doses and dose reductions and/or treatment holds, if indicated.
- 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 UCSF IRB, Sponsor, and FDA (if applicable).
- Adherence to patient follow-up requirements.

After completion of the auditing visit, the assigned DSMC Monitor/Auditor will meet in person with the HDFCCC CRC, PPM (if a regulatory annual was performed), and the PI (if there are significant findings) and remotely with the participating site study team at the end of the monitoring visit to review the follow-up action items. For Safety Lead-In Cohorts, the HDFCCC PI and study team representative must complete the Study Status Report and submit to the DSMC Chair and Director requesting for safety review and approval of this cohort prior to further enrollment in the trial. The DSMC will grant approval of this Safety Lead-In request within 48 hours if there aren't any significant safety issues (i.e., undocumented SAEs, protocol violations, etc.) in this safety cohort audited.

Following the completion of the auditing visit, the DSMC Monitor/Auditor will complete the Monitoring Visit Report (MVR), which describes the findings of this auditing 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 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 response to the DSMC required.
- Unsatisfactory, halt enrollment of new subjects, corrective action plan required within 10 days to the DSMC. The DSMC Chair will notify the IRB regarding the results of this audit/monitoring visit.

The MVR Report is then signed electronically or via wet ink signature by the DSMC Monitor/Auditor, DSMC Supervisor, DSMC Director, and the DSMC Chair or Vice Chair and then is sent to the HDFCCC PI, CRC, CRM, PPM (for regulatory reviews only) and the participating site's Investigator and study team representative within 20 business days of

completion of the auditing visit. This report is then forwarded to the assigned Associate Director (as per the HDFCCC Point of Contact Listing) for follow-up/review. Additionally, the signed MVR is scanned into the PC console under "documents" in OnCore and is filed in the internal DSMC electronic files. The signed copy of this MVR, along with a copy of the e-mail of the report to the PI and study team, and the completed DSMC Monitoring/Auditing Checklist is provided to the DSMC Director for inclusion to 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. The MVR has a separate Word document for the completion of the action items by the UCSF or participating site study team, which requires an electronic or wet ink signature by the study team member completing these items. The DSMC Monitor/Auditor will then sign electronically, or via wet ink signature, this Word document to confirm completion of all action items. The assigned DSMC Monitor/Auditor will also verify that the amended eCRFs in OnCore have been adequately addressed by the study team and will then will "validate" each amended eCRF. If queries are not resolved prior to the next scheduled auditing visit, the assigned DSMC Monitor/Auditor will let the PI, assigned CRC, and study team or participating site staff member know that further enrollment in this trial may be suspended by the DSMC until all queries are resolved.

Alternate Procedures

There are no alternate procedures to this policy.

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 CRF 312.50.
- 21 CFR 812.40.

Policy Approval

This policy document was approved by the following personnel on the following dates:

DocuSigned by:
Kate Shumate
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1/24/2020

Kate Shumate, MPA, CCRP
Chief of Staff
Director, Administration and Planning
Helen Diller Family Comprehensive Cancer Center

Date

DocuSigned by:
Thierry Jahan
F67EAB476220482...

1/27/2020

Thierry Jahan, MD — Date
Professor of Medicine
Chair, Data and Safety Monitoring Committee
Helen Diller Family Comprehensive Cancer Center

DocuSigned by:
Eric Small
7FCB32D327E3438...

2/2/2020

Eric Small, MD — Date
Chief Scientific Officer
Helen Diller Family Comprehensive Cancer Center

Policy Coordinator:

John McAdams
DSMC Director
John.mcadams@ucsf.edu

University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
Policy and Procedure

Policy Title:	**Policy for Data and Safety Monitoring of Phase 2 or 3 Single-Site and Multicenter Institutional Investigator-Initiated Trials**
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Version Number:	Revision 2

Notes: Page number corresponds to page number in updated version (Revision 3).
New text in modified paragraphs is shown as ***bold italics*** and deleted text is shown as ~~strikethrough~~.

Page No.: 1	**Section**: Purpose/Scope/Background

Original Text	**Purpose** This policy defines the process by which therapeutic or non-therapeutic Phase 2 or 3 Multicenter Investigator-Initiated oncology clinical trials at the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) are audited by the Data and Safety Monitoring Committee (DSMC) Monitors/Auditors. **Background** The Data and Safety Monitoring Committee (DSMC) Monitors/Auditors are responsible for monitoring/auditing institutional clinical trials for data validity, trial conduct, and serious adverse event (SAE) reporting. The risk assessment of the study is determined by the phase of the trial, which in turn, designates the frequency of monitoring/auditing on the trials. The study patient files from both the Coordinating Site and the Participating Site(s) for Multicenter Phase 2 or 3 trials are audited twice per year, dependent upon accrual, with twenty percent of the study patients at each site audited, or at least three study patients per site, if the calculated value is less than three. For “greater than minimal risk” Phase 2 or 3 nontherapeutic trials, 20% of the enrolled study participants will be audited once per year. If 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 Regulatory files in iRIS will be reviewed at each auditing visit, while a complete Regulatory Audit of the Coordinating Site and the Participating Site(s) will be performed on a yearly basis.

New Text	**Purpose** This policy defines the process by which interventional therapeutic Phase 2 Single and Multicenter Site Institutional oncology clinical trials at the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) are audited by the Data and Safety Monitoring Committee (DSMC) Monitors/Auditors. **Background** The HDFCCC DSMC Monitors/Auditors are responsible for providing monitoring/auditing for all interventional therapeutic and non-therapeutic institutional 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 monitoring/auditing for each trial. In general, the HDFCCC participant "shadow charts" for single site and multicenter site Phase 2 trials are audited on a semiannual basis, dependent upon accrual, beginning within one month of the initiation of enrollment in the trial. The participating site's source documents are audited remotely via either review of redacted source documents downloaded by the site into the PC console of OnCore or via access to the site's electronic medical records. For "greater than minimal risk" Phase 2 or 3 nontherapeutic trials, 20% of the enrolled study participants are audited once per year. If 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. A limited regulatory review in iRIS occurs at each scheduled auditing visit to review items such as the approved protocol and ICF versions, along with the Delegation of Authority Form and the FDA 1572 forms, while a complete regulatory audit reviewing all regulatory documents is performed on an annual basis.
Reason for Change	Added Scope section and updated/modified this section for clarity.

Page No.: 1-2	**Section**: Procedures

Original Text	**Procedure** 1. A DSMC Monitor is assigned to that study by the DSMC Manager (or DSMC Manager) will audit this trial. 2. The assigned Clinical Research Coordinator (CRC) will notify the assigned DSMC Senior Monitor/Auditor or DSMC Manager when the Phase 2 or 3 trial starts enrolling study patients. The assigned DSMC Senior Monitor/Auditor or DSMC Manager will ensure that all trial data for each study patient enrolled at UCSF (Coordinating Site) or the Participating Sites is entered in OnCore® (clinical trials data management system). 3. All patient data must be entered in OnCore before the DSMC Senior Monitor/Auditor can schedule an auditing visit with the CRC and study team at UCSF and/or the Participating Sites. a. The assigned DSMC Senior Monitor/Auditor or DSMC Manager will also contact the UCSF Coordinating Site CRC by phone or e-mail for updates in study enrollment/OnCore data entry as well. 4. When it is determined that auditing is required, the assigned DSMC Senior Monitor/Auditor or the DSMC Manager will e-mail the PI, assigned CRC and study team to schedule an auditing visit. Once the auditing visit date is scheduled, a formal e-mail is sent to the Principal Investigator (PI) and study team members, including the assigned CRC, regarding the details of this visit, including the number of study patients to be monitored. Additionally, the Regulatory documents in iRIS will be reviewed at each monitoring visit, while a Regulatory Audit will be performed on a yearly basis. For Phase 2 or 3 therapeutic trials, the DSMC Monitor/Auditor audits twenty percent of the study patients, or at least three study patients if the calculated value is less than three, twice per year. For “greater than minimal risk” Phase 2 or 3 nontherapeutic trials, the DSMC Monitor/Auditor audits 20% of the study patients once per year. If tissue banking trials are determined to be “greater than minimal risk”, the DSMC Monitor/Auditor will only review Serious Adverse Events (SAEs) recorded in OnCore at each DSMC Meeting.

New Text	**Procedures** The DSMC Supervisor or Director assigns a DSMC Senior Monitor/Auditor for each Investigator Initiated Trial (IIT) at the time of Protocol Review Committee (PRC) approval. The assigned Clinical Research Coordinator (CRC), Clinical Research Manager (CRM), or Protocol Project Manager (PPM) will notify the assigned DSMC Senior Monitor/Auditor when the Phase 2 or 3 trial has started enrollment. Additionally, the CRC or CRM will notify the assigned DSMC Senior Monitor/Auditor when the Site Initiation Visit (SIV) with the participating site(s) is scheduled so the DSMC Senior Monitor/Auditor can attend to ensure that the auditing process is clearly communicated to the participating site staff. The assigned DSMC Senior Monitor/Auditor will review trial enrollment in OnCore in order to schedule an auditing visit with the study team. All participant study data at the HDFCCC and participating site(s) must be entered in OnCore or an approved Electronic Data Capture (EDC) system by the study team prior to the DSMC Senior Monitor/Auditor scheduling an auditing visit with the study team at either site. For safety lead-in cohorts, the assigned CRC will notify the assigned DSMC Senior Monitor/Auditor in order to ensure scheduling of an auditing visit for all study participants in the safety lead-in cohort prior to safety review request by the Principal Investigator (PI) and study team to the DSMC Chair and DSMC Director. The assigned DSMC Senior Monitor/Auditor will notify the HDFCCC PI, assigned CRC, and CRM and the participating site Investigator and study team members in order to schedule a subject auditing visit. The HDFCCC PPM or participating site regulatory contact is notified for regulatory audits. Once the monitoring visit date is scheduled, the HDFCCC PI and study team members and the participating site Investigator and study team members are notified regarding the details of this visit, including the number of participants to be audited. A limited regulatory review in iRIS occurs at each scheduled auditing visit to review items such as the approved protocol and ICF versions, along with the Delegation of Authority Form and the FDA 1572 forms, while a complete regulatory audit reviewing all regulatory documents is performed on an annual basis. In general, the HDFCCC participant “shadow charts” for single site and multicenter site Phase 2 trials are audited on a semiannual basis, dependent upon accrual, beginning within one month of the initiation of enrollment in the trial. The participating site’s source documents are audited remotely via either review of redacted source documents downloaded by the site into the PC console of OnCore or via access to the site’s electronic medical records. For “greater than minimal risk” Phase 2 or 3 nontherapeutic trials, a random selection by the assigned DSMC Senior Monitor/Auditor of 20% of the enrolled study participants are audited once per year. If 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.

Reason for Change	Updated and modified this section for clarity.

Page No.: 3,4	**Section**: Procedures
Original Text	i. The CRC will notify the assigned DSMC Senior Monitor/Auditor or DSMC Manager when eCRF queries have been addressed (should be completed prior to the next Auditing Visit). ii. The assigned DSMC Senior Monitor/Auditor or DSMC Manager will check the amended eCRFs and validate eCRFs in which all queries have been resolved. The eCRFs can only be validated by the assigned DSMC Senior Monitor/Auditor or DSMC Manager; therefore, all queries will be addressed before an eCRF can be validated. If queries are not resolved by the next monitoring visit, the assigned DSMC Senior Monitor/Auditor or DSMC Manager will let the PI, assigned CRC, and study team member know that future enrollment in this trial may be held until this date is entered and queries resolved. All queries must be validated by the assigned DSMC Monitor/Auditor or DSMC Manager before the closeout of the study. b. The Audit Report: i. The assigned DSMC Senior Monitor/Auditor or DSMC Manager will work with the assigned CRC and PPM to resolve as many of the items/issues encountered during the auditing visit. All remaining items will be entered on the Final Monitoring Report and provided to the PI, assigned CRC, and PPM (for regulatory reviews only). All findings from the auditing of the subject files will the responsibility of the CRC to resolve, while all findings from the auditing of the regulatory binders will be the responsibility of the Protocol Project Manager (PPM) and the study team to resolve. ii. The Final Report will be due within 30 days of the monitoring visit and this report must be signed in pen or via DocuSign by the DSMC Senior Monitor/Auditor, DSMC Manager, and the DSMC Chair and then will be sent to the PI, CRC, PPM (for regulatory reviews only), and the assigned Research Personnel Manager (RPM). For participating Site Audits, the Final Monitoring Report will be sent to the Investigator and CRC at the site and cc'd to the Coordinating Site CRC, PPM (if applicable), RPM, and PI. Additionally, the signed Final Report will be scanned into OnCore® and filed in the DSMC electronic files.

New Text	• Informed consent forms, HIPAA, and Bill of Rights documents properly obtained. • All required pre-study tests and procedures are obtained and reviewed by the PI prior to the start of treatment. • All eligibility criteria reviewed to ensure that the study patient is qualified for the trial. • Adherence to treatment plan is documented, including Investigational Product (IP) orders, drug doses and dose reductions and/or treatment holds, if indicated. • 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 UCSF IRB, Sponsor, and FDA (if applicable). • Adherence to patient follow-up requirements. After completion of the auditing visit, the assigned DSMC Senior Monitor/Auditor will meet in person with the HDFCCC CRC, PPM (if a regulatory annual was performed), and the PI (if there are significant findings) and remotely with the participating site study team at the end of the monitoring visit to review the follow-up action items. For Safety Lead-In Cohorts, the HDFCCC PI and study team representative must complete the Study Status Report and submit to the DSMC Chair and Director requesting for safety review and approval of this cohort prior to further enrollment in the trial. The DSMC will grant approval of this Safety Lead-In request within 72 hours if there aren't any significant safety issues (i.e., undocumented SAEs, protocol violations, etc.) in this safety cohort audited. Following the completion of the auditing visit, the DSMC Senior Monitor/Auditor will complete the Monitoring Visit Report (MVR), which describes the findings of this auditing 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 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 response to the DSMC required. • Unsatisfactory, halt enrollment of new subjects, corrective action plan required within 10 days to the DSMC. The DSMC Chair will notify the IRB regarding the results of this audit/monitoring visit. The MVR Report is then signed electronically or via wet ink signature by the DSMC Senior Monitor/Auditor, DSMC Supervisor, DSMC Director, and the DSMC Chair or Vice Chair and then is sent to the HDFCCC PI, CRC, CRM, PPM (for regulatory reviews only) and the participating site's Investigator and study team representative.

Reason for Change	Modified and updated this section for clarity