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

Policy for Data and Safety Monitoring of Phase 1 Single Site and Multicenter Trials

Purpose

This policy defines the process by which interventional therapeutic Phase 1 Single and Multicenter Site oncology clinical trials at the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) are monitored 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 or multicenter site Phase 1 trials are monitored monthly, dependent upon accrual, beginning within one month of the initiation of enrollment in the trial. The participating site's source documents are monitored 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. A limited regulatory review occurs at each scheduled monitoring visit, 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 regulatory contact will notify the assigned DSMC Senior Monitor/Auditor when the Phase 1 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 monitoring process is clearly communicated to the participating site staff. The assigned DSMC Monitor/Auditor will review trial enrollment in OnCore in order to schedule a monitoring 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 a monitoring visit with the study team at either site. For accelerated dose titration and intrapatient dose titration trials, the assigned CRC will notify the assigned DSMC Monitor/Auditor in order to

ensure scheduling of a monitoring visit for all study participants in a dosing cohort prior to dose escalation request by the Principal Investigator (PI) and study team to the DSMC Chair and DSMC Director.

The assigned DSMC Monitor/Auditor notifies the HDFCCC PI, assigned CRC, and CRM and the participating site Investigator and study team members in order to schedule a participant monitoring visit. The HDFCCC regulatory contact 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 monitored. A limited regulatory review occurs at each scheduled monitoring 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. For Phase 1 trials, all participants enrolled are monitored on a monthly basis, depending on study accrual, through the Dose Limiting Toxicity (DLT) period of the trial up until the maximum tolerated dose (MTD) is determined. Once the MTD is determined and the trial is in the dose expansion phase, the trial will then be audited biannually, with 20 percent of the enrolled study patients audited for the first two cycles of treatment.

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 is complete for all participants to be monitored 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 monitor 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 monitoring 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).
- Review of possible dose limiting toxicities (DLTs).
- Adherence to patient follow-up requirements.

After completion of the monitoring visit, the assigned DSMC Monitor/Auditor will meet in person with the HDFCCC CRC, regulatory contact (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 Dose Escalation Visits, the HDFCCC PI and study team representative must complete the Study Status Report and submit to the DSMC Chair and Director requesting for dose escalation prior to enrollment of the next cohort as per protocol. The DSMC will grant approval of this dose escalation request within 48 hours if there aren't any significant safety issues (i.e., undocumented DLTs, SAEs, protocol violations, etc.) in the patient dosing cohort that was monitored.

Following the completion of the monitoring visit, the DSMC Monitor/Auditor will complete the Monitoring Visit Report (MVR), 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 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, regulatory contact (for regulatory reviews only) and the participating site's Investigator and study team representative within 20 business days of completion of the monitoring 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 verify that the amended eCRFs have been adequately addressed by the study team and will then "validate" each amended eCRFs. If queries are not resolved prior to the next scheduled monitoring visit, 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 will not be granted 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:
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12/13/2019

Kate Shumate, MPA, CCRP
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Date

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Helen Diller Family Comprehensive Cancer Center
Policy and Procedure

Policy Title:	**Policy for Data and Safety Monitoring of Phase I Single-Site and Multicenter Institutional Investigator-Initiated Trials**
Version Date:	07November2019
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 Phase 1 Single Site Investigator-Initiated oncology clinical trials at the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) are monitored 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 on the studies. The study patient files for single-site Phase 1 trials are monitored monthly, dependent upon accrual, beginning within one month of the initiation of enrollment. The Regulatory files in iRIS will be reviewed at each monitoring visit, while a complete Regulatory Audit will be performed on a yearly basis.

New Text	**Purpose** This policy defines the process by which interventional therapeutic Phase 1 Single Site Institutional oncology clinical trials at the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) are monitored 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 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 multicenter site Phase 1 trials are monitored monthly, dependent upon accrual, beginning within one month of the initiation of enrollment in the trial. The participating site's source documents are monitored 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. A limited regulatory review in iRIS occurs at each scheduled monitoring 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). 2. The assigned Clinical Research Coordinator (CRC) or Protocol Project Manager (PPM) will notify the assigned DSMC Senior Monitor/Auditor or DSMC Manager when the Phase 1 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 in 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 a monitoring visit with the CRC and study team. a. The assigned DSMC Senior Monitor/Auditor or DSMC Manager will also contact the CRC by phone or e-mail for updates in study enrollment/OnCore data entry as well. b. For accelerated dose titration and intrapatient dose titration trials, the assigned CRC will notify the assigned DSMC Senior Monitor/Auditor or DSMC Manager so that a monitoring visit can be scheduled to ensure that all study patients in a dosing cohort will be monitored prior to dose escalation request by the PI and study team to the DSMC Chair and Manager. 4. When it is determined that monitoring is required, the assigned DSMC Senior Monitor/Auditor or the DSMC Manager will e-mail the PI, assigned CRC and study team to schedule a monitoring visit. Once the monitoring 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 1 studies, the study patients will be monitored on a monthly basis, depending on study accrual, through the Dose Limiting Toxicity (DLT) period. When the Maximum Tolerated Dose (MTD) is reached, the trial will then be audited twice per year with 20 percent of the enrolled study patients monitored for the first two cycles of treatment. .

New Text	**Procedures** The DSMC Supervisor or Director assigns a DSMC Monitor/Auditor for each 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 1 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 monitoring 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 a monitoring 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 a monitoring visit with the study team at the HDFCCC site or the participating site. For accelerated dose titration and intrapatient dose titration trials, the assigned CRC will notify the assigned DSMC Senior Monitor/Auditor in order to ensure scheduling of a monitoring visit for all study participants in a dosing cohort prior to dose escalation request by the Principal Investigator (PI) and study team to the DSMC Chair and DSMC Director. The assigned DSMC Senior Monitor/Auditor notifies the HDFCCC PI, assigned CRC, and CRM and the participating site Investigator and study team members in order to schedule a subject monitoring 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 monitored. A limited regulatory review in iRIS occurs at each scheduled monitoring 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. For Phase 1 trials, the participants are monitored on a monthly basis, depending on study accrual, through the Dose Limiting Toxicity (DLT) period of the trial up until the maximum tolerated dose (MTD) is determined. Once the MTD is determined, the trial will then be audited biannually, with 20 percent of the enrolled study patients audited for the first two cycles of treatment.

Reason for Change	Updated and modified this section for clarity.

Page No.: 3,4	**Section**: Procedures

Original Text	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 Monitoring 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 dose escalations will not be granted until the queries are resolved. All queries must be validated by the assigned DSMC Monitor/Auditor or DSMC Manager before the closeout of the study. b. The Monitoring 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 monitoring 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 monitoring of the subject files will the responsibility of the CRC to resolve, while all findings from the monitoring 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) Additionally, the signed Final Report will be scanned into OnCore®.

New Text	• Informed consent forms, HIPAA, and Bill of Rights documents properly obtained. • Any 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). • Review of possible dose limiting toxicities (DLTs). • Adherence to patient follow-up requirements. After completion of the monitoring visit, the assigned DSMC Senior Monitor/Auditor will meet with the CRC, PPM (if a regulatory annual was performed), and the PI (if there are significant findings) at the end of the monitoring visit to review the follow-up action items. For Dose Escalation Visits, the assigned CRC and the Pi must complete the Study Status Report and submit to the DSMC Chair and Director requesting for dose escalation. The DSMC will grant approval of this dose escalation request within 72 hours if there aren't any significant safety issues (i.e., undocumented DLTs, SAEs, protocol violations, etc.) in the patient dosing cohort that was monitored. Following the completion of the monitoring visit, the DSMC Monitor/Auditor will complete the Monitoring Visit Report (MVR), which describes the findings of this monitoring visit. The study is given an overall evaluation by the DSMC Monitor (and approved by the DSMC Supervisor, Director, and 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 DSMC • Unsatisfactory, halt enrollment of new subjects, corrective action plan required within 10 days to the DSMC.
Reason for Change	Modified and updated this section for clarity