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 that are deemed above minimal risk 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. All institutional phase I therapeutic dose escalation trials are designated with a high-risk assessment; therefore, the electronic and/or paper source documents for all enrolled participants in each dosing cohort is monitored (as per accrual) by a DSMC Monitor/Auditor prior to approval of the dosing cohort, and includes a review of all study information through the first post-Dose Limiting Toxicity (DLT) visit 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 participants audited for the first five cycles of treatment. DSMC Monitor/Auditors will send a follow-up report 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 this report within 20 business days. 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.

Procedures

The DSMC Monitoring Supervisor will assign a DSMC Monitor/Auditor for each Investigator Initiated Trial (IIT) at the time of Protocol Review and Monitoring Committee (PRMC) approval as per notification from an automatic OnCore report. The assigned DSMC Senior Monitor/Auditor will receive notification from OnCore when the Phase 1 trial has started accrual in the trial. The CRC or other study team member 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 be in communication with the assigned CRC and review trial enrollment in OnCore in order to schedule monitoring visits for this trial. The assigned DSMC Monitor/Auditor will receive notification from OnCore when each participant has been enrolled in this trial in order to schedule monitoring visits for each dosing cohort. 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 monitoring visit with the study team.

The assigned DSMC Monitor/Auditor will send a formal notification to the HDFCCC PI, assigned CRC, and CRM (and the participating site Investigator and study team members) prior to the monitoring visit. The HDFCCC or participating site regulatory contact will be notified for biennial regulatory audits.

At each participant monitoring visit, a limited regulatory review will occur, which will include the approved protocol and ICF versions, along with the Delegation of Authority Form, the FDA 1572 form, etc.. The formal regulatory audits will include a review of all regulatory documents for the trial on a biennial basis.

On each day of the monitoring visit, 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 DSMC Monitor/Auditor will remotely review the electronic (stored on Secure Box, Complion, Share Point, OnCore, or Veeva Vault, and/or paper source documents scanned securely. If the DSMC Monitor/Auditor is conducting an on-site monitoring visit, then the charts will be reviewed at either the space where the charts are maintained or at their workstations. These paper source documents 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 CRA console of OnCore, Veeva Vault, or securely e-mailed to the DSMC Monitor/Auditor and/or the site’s Electronic Medical Record (EMR). The DSMC Monitor/Auditor will also 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 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) 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) and the Follow-up Action Items Report, 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 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 Follow-up Action Item Report) 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 HDFCCC 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 on the follow-up action items report and provide to the assigned DSMC Monitor/Auditor once completed. The DSMC Monitor/Auditor will then sign electronically sign this follow-up action items report 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

- 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:

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Policy Title: Policy for Data and Safety Monitoring of Phase I Single-Site and Multicenter Institutional Investigator-Initiated Trials

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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.
**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.

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**Reason for Change**

Updated/modified this section for clarity.
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.
New Text

The DSMC Monitoring Supervisor will assign a DSMC Monitor/Auditor for each Investigator Initiated Trial (IIT) at the time of Protocol Review Committee (PRC) approval as per notification from an automatic OnCore report. The assigned Clinical Research Coordinator (CRC), or other study team member will notify the assigned DSMC Senior Monitor/Auditor when the Phase 1 trial has started accrual in the trial. Additionally, the CRC or other study team member 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 be in communication with the assigned CRC and review trial enrollment in OnCore in order to schedule monitoring visits for this trial. 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 monitoring visit with the study team. 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 will send a formal notification to the HDFCCC PI, assigned CRC, and CRM (and the participating site Investigator and study team members) prior to the monitoring visit. The HDFCCC or participating site regulatory contact will be notified for biennial regulatory audits.

At each participant monitoring visit, a limited regulatory review will occur, which will include the approved protocol and ICF versions, along with the Delegation of Authority Form, the FDA 1572 form, etc. The formal regulatory audits will include a review of all regulatory documents for the trial on a biennial basis.

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| Reason for Change | Updated and modified this section for clarity. |