1. BACKGROUND:

The Dana-Farber/Harvard Cancer Center's (DF/HCC) Data and Safety Monitoring Committee (DSMC) is charged with providing ongoing data and safety monitoring for ~~high~~ greater than minimal risk: Pilot, Phase I ~~and~~, Phase II and Phase I/II clinical trials initiated and conducted by DF/HCC investigators. The primary purpose of the committee is to review the overall progress of the trial to ensure the safety of study participants, appropriate oversight by the sponsor-investigator, and data compliance.

The DSMC has authority to intervene in the conduct of these studies as ~~well as evaluate~~necessary to ensure the ~~overall progress~~safety of the ~~trial~~ participants and to maintain the highest quality clinical research data. The DSMC is an oversight committee and an integral component of DF/HCC's Data and Safety Monitoring Plan.

Commented [C1]: Updated with table in section 3.3.4. to clearly outline data compliance thresholds, areas of committee focus (toxicity) and action(s) that will be taken by the DSMC at each level of non-compliance. A table has been inserted to clearly outline these details.

2. ASSOCIATED DF/HCC POLICIES:

2.1. COM-100
2.2. DATA-100

3. PROCEDURE:

3.1. Protocols Requiring Monitoring:

3.1.1. The Scientific Review Committees (SRC and PSRC), Institutional Review Board (IRB) and/or the ~~Clinical Investigations Leadership~~Executive Committee ~~(CLC~~for Consortium Clinical Research (ECCCR) will identify high-risk DF/HCC initiated protocols.

3.1.1.1.High Risk protocols include, but are not limited to:

- DF/HCC investigator-sponsored interventional trials, DF/HC multi-center trials, DF/HCC held IND/IDE trials
- First in human and/or pediatric clinical trials that do not have an established DSMC
- Gene transfer protocols that do not have an established DSMC
- Vaccine trials using live or attenuated viruses that do not have an established DSMC
- Other unusually complex or intensive protocols requiring a DSMC as determined by the SRC, PSRC, IRB and/or CLC

3.1.1. High-risk, externally sponsored trials must have a designated DSMC or appropriate Data and Safety Monitoring plan in place. The protocol-specific Data Safety Monitoring Plan (DSMP) must be reviewed and approved by the IRB of record prior to activation of the protocol. The DFCI IRB may require additional documentation from external sponsors to ensure the oversight is appropriate. The DF/HCC DSMC will not act as the oversight committee for trials under a non-

DF/HCC regulatory sponsor. However, if directed by the SRC, IRB and/or CLC, the DF/HCC DSMC may monitor the local conduct *only* for high-risk, externally-sponsored protocols.

3.2. **Protocol Review Procedures:**

3.2.1. The DSMC meets monthly to review ~~toxicity, data submission compliance and accrual~~study progress. Protocols are typically reviewed every 3, 6 or 9 months based on the protocol status, accrual rate, and review of ongoing safety indicators.

3.2.2. ODQ notifies the Sponsor-Investigator and designated sponsor personnel of the next upcoming DSMC review for a given protocol. Notifications are typically sent 4-6 weeks prior to the scheduled review date.

3.2.3. The sponsor-investigator, or designee, will submit the ~~following~~completed DSMC monitoring form, with any required attachments, and the DSMC Data and Missing Forms Report from InForm, when applicable, to ODQ to facilitate review by the DSMC~~:~~.

- ~~Completed DSMC Monitoring Form~~
- ~~DSMC Data and Missing Forms Report~~
- ~~Multi-Center Progress Report (attached to DSMC Monitoring Form, for investigator-sponsored, multi-center trials only)~~

In addition, ODQ will prepare the following information to facilitate review by the DSMC:

- Protocol Summary and Registration Report
- OHRS Summary Report

3.2.4. The DSMC reviews toxicity data and SAEs, protocol and subject deviations, and monitoring reports in addition to the information provided on and attached to the DSMC monitoring form by the investigator and research team. The DSMC will make a determination as to whether the protocol it is safe and appropriate for the protocol to continue as written. The DSMC may make recommendations to the sponsor-investigator, require changes to the research protocol, request an internal audit, or request suspension of a research protocol when appropriate.

3.2.5. For protocols currently open to accrual: When the DSMC requests a suspension, ODQ will submit a request to the IRB to temporarily suspend new accruals for the entire protocol or individual site(s), as determined by the DSMC.

3.2.6. For protocols closed to accrual: When the DSMC requests a suspension, ODQ will submit a request to the IRB to suspend research activities under the protocol or at individual site(s), as determined by the DSMC.

3.3. **Data Compliance:**

~~3.2.4.~~3.3.1. The sponsor-investigator is responsible for data compliance of all participating sites both within and outside DF/HCC ~~for PI-Initiated research.~~. The ~~DF/HCC~~ sponsor-investigator, or designee, is asked to provide the DSMC ~~has the prerogative to review data~~with a copy of the missing forms report as part of the DSMC submission materials in order to demonstrate compliance ~~at any time, regardless of the next scheduled review.~~with DSMC guidelines.

3.3.2. The DSMC ~~defines data submission~~ coordinator in ODQ will notify study teams if they submit a missing forms report showing that the study is out of compliance ~~as less than or equal to 10% of total forms missing for both overall protocol~~ .

3.3.3. The DF/HCC DSMC has the prerogative to review data compliance ~~and site-specific~~at any time, regardless of the timing of the next scheduled review.

~~3.2.4.1.~~To assess data compliance~~. Toxicity reporting, as a sub-category of missing forms, will also be held~~, the DSMC follows the guidelines in the table below. However, the DSMC has discretion to ~~the less than or equal~~deviate from the guidelines below as necessary to ~~10% threshold for site-specific compliance.~~

~~3.2.5.~~3.3.4. ~~In the event the percentage of total missing forms or site-specific toxicity forms is greater than 10%, but~~ensure data integrity or when the total of number of forms missing is small~~, the DSMC Chair has the discretion to deem the protocol compliant~~.

~~3.2.6. When protocols are identified as non-compliant with data submission, the following procedures, dependent on the percentage of missing forms, will be followed.~~

~~3.2.6.1.If a protocol has > 10% but <20% of total forms missing for the overall protocol or toxicity forms missing at any one site:~~

~~3.2.6.1.1. Notice of percentage of forms missing and a reminder of data submission compliance criteria will be incorporated into the DSMC response memos.~~

Missing Forms Report (MFR)	MFR Compliance Threshold	Action by DSMC
Total forms; all sites	>10% outstanding forms	First Occurrence: Notice of non-compliant forms and re-review by DSMC in 3 months. If remains non-compliant at 3-month review: Notice of 2-week warning and possible suspension (protocol or site) if data is not in compliance within 2-weeks.
Total forms; individual site	>10% outstanding forms	
Treatment, Toxicity or Post Treatment Toxicity forms for entire protocol or at an individual site*	>10% outstanding forms	
Total forms; all sites	>20% outstanding forms	Notice of 2-week warning and possible suspension (protocol or site) if data is not in compliance within 2-weeks.
Total forms; individual site	>20% outstanding forms	
Toxicity or Post Treatment Tox forms for entire protocol or at an individual site*	>20% outstanding forms	

* Other forms that directly impact subject safety may also be held to this standard as determined by the study design

~~3.2.6.1.2. The protocol will be given a 3-month review. At the time of the 3-month review:~~

~~3.2.6.1.2.1.If the protocol data is compliant, the protocol will be assigned its next review date based on DSMC recommendation of the safety review.~~

~~3.2.6.1.2.2.If the protocol remains non-compliant, an email memo will be sent no later than the next business day to the sponsor-investigator, designated research team member and applicable clinical trials office defining deadlines for data submission compliance and consequences for failure to comply. Data must be compliant (<10% of total forms missing and <10% of site-specific toxicity forms missing) within 2 weeks after the DSMC meeting.~~

~~3.2.6.2.If the protocol has >20% of total forms missing for the protocol or toxicity forms missing at any one site:~~

~~3.2.6.2.1. An email memo will be sent no later than the next business day (Monday – Friday) to the sponsor-investigator, designated research team member, and applicable clinical trials office defining deadlines for data submission compliance and consequences for failure to comply. Data must be compliant (<10% of forms missing) within 2 weeks after the DSMC meeting.~~

~~3.2.6.3.If a 2-week data compliance deadline is not met, the following actions will be applied:~~

~~3.2.6.3.1. For protocols open to accrual where the overall % of missing forms is out of compliance, accrual will be suspended at **ALL** sites. On behalf of the DSMC, ODQ will submit a Closure to Accrual form to the Institutional Review Board (IRB).~~

~~3.2.6.3.2. For protocols open to accrual where a specific site(s) is out of compliance, accrual will be suspended at the specific site(s). On behalf of the DSMC, ODQ will submit a closure to accrual request to the Institutional Review Board (IRB).~~

~~3.2.6.3.3. For protocols already closed to accrual, the ODQ DSMC coordinator will send a memo to the Director of the Office for Human Research Studies (OHRS) recommending suspension of activity on any pending protocols of the sponsor-investigator.~~

~~3.2.6.4.~~No data analysis, abstract, or publication may take place while a protocol is out of data compliance~~.~~

~~3.2.6.5.~~3.3.4.1. ~~The DSMC Chair has the discretion to adjust the timeframes listed above~~ without approval from the DSMC Chairs.

~~3.3.~~3.4. Committee Membership and Meeting Logistics

~~3.3.1.~~3.4.1. Committee members are appointed by the Senior VP for Research and will include at a minimum:

Voting Members:

- [3] Medical Oncologists (including the committee Chair)
- [1] ad hoc Physician as needed (Radiation Oncologist, Surgeon, etc)
- [1] Biostatistician
- [1] Nurse
- [1] Pharmacist

Non-voting Member:

- [1] Meeting Coordinator

~~3.3.2.~~3.4.2. ODQ will maintain DSMC meeting minutes and correspondence. The DSMC minutes are reviewed and approved by the DSMC chairs prior to finalization. The final minutes, and any recommendations made to study teams ~~and reported to~~, are shared with the IRB ~~and the Clinical Investigations Leadership Committee (CLC). A summary of all DSMC activity is reviewed by CLC~~Chairs monthly.

3.4.3. All trial and participant information will remain confidential.

~~3.3.3.~~3.4.4. Members of the DSMC will not participate in the review of any protocol where they are an investigator and must not have a direct interest in knowing or influencing trial outcome or have a financial or intellectual interest in the outcome of this study. Members must disclose all potential conflicts of interest, including financial interests or relationships with any supporting pharmaceutical or biotechnology companies. All DSMC members are required to sign a Confidentiality and Conflict of Interest (COI) Statement related to the trials discussed. Members will recuse themselves from the discussion and voting if a conflict exists for a given protocol.