DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH

TITLE: Research Conduct Oversight by External Sponsors		
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1. POLICY STATEMENT:

The DF/HCC understands that external sponsors are required to monitor the progress of clinical investigations and ensure appropriate research data collection and overall research conduct activities in accordance with the protocol and federal regulations. This policy ensures that the DF/HCC appropriately balances the need to accommodate these activities by external sponsors with constraints on staffing, work schedules, and space.

Commented [SC1]: Edits throughout to remove old terminology and clarify responsibilities of PI and study team at each participating DF/HCC site, including the Core Site.

2. BACKGROUND:

Sponsors are responsible for ensuring proper monitoring of the investigation (21 CFR 312.50, 21 CFR 812.40) and selecting monitors that are qualified by training and experience (21 CFR 312.53, 21 CFR 812.43).

3. RESPONSIBLE PERSONNEL:

3.1. ~~Overall~~ Principal Investigator (PI)
3.2. Study Coordinator
3.3. Clinical Trial Monitor

4. DEFINITIONS:

4.1. **Study Coordinator:** The person responsible for entering the data onto case report forms and for maintaining the regulatory binder, regardless of his/her title.

4.2. **Clinical Trial Monitor (or Monitor):** The person responsible for monitoring the data on behalf of the sponsor or contract research organization.

4.3. **Monitoring Visits:** The act of overseeing the progress of a clinical trial (in real time) and of ensuring that the trial is conducted, recorded, and reported in accordance with the protocol. This does not include visits for a Quality Assurance audit by the sponsor or regulatory agency inspections.

1.1. ~~Lead~~**Core Site**~~:~~ – The core site ~~at~~is the ~~same physical location as the Overall PI.~~ designated DF/HCC site that coordinates regulatory submissions for DF/HCC.

~~1.1.~~1.2. **Site Qualification Visit (SQV):** A visit conducted by a sponsor representative to ensure the prospective investigator and investigative site are fully capable and equipped to run the specific protocol.

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Effective Date: 1/31/20
Last Reviewed Date: 11/12/19

~~1.2.~~1.3. **Site Initiation Visit (SIV):** A visit conducted by a sponsor representative to review the specifics of the protocol (i.e., the science, design, procedures, safety reporting and case report form completion) in preparation to screen and enroll the first subject.

~~4.5.~~1.4. **Case Report Form (CRF):** A printed, optical or electronic document designed to record all of the protocol required information to be reported to the Sponsor on each trial subject.

~~4.6.~~1.5. **Data Lock:** The predetermined time and date after which the sponsor will not accept additional subject data for the database. This may occur at the time of interim analysis or at the end of the research when the database is considered complete.

5. POLICY:

5.1. Site Qualification Visit (SQV)

5.1.1. When a SQV by an external sponsor is scheduled, ~~the lead site~~each study team will ~~attempt to~~ coordinate the visit ~~between the DF/HCC sites. There may be a need for a SQV~~ at each participating DF/HCC site.

~~5.1.2. The SQV is scheduled with the Overall PI, Clinical Research Lab and the Pharmacy (if applicable). Other pertinent departments or individuals, expected to participate in the protocol, may be included.~~

~~5.1.3.~~5.1.2. ~~The Overall~~The PI or designated research team member conducts the visit with the sponsor representative, reviews departmental procedures, and answers any questions the sponsor representative may have during the mutually agreed upon time frame. A member of the research team must be present for the entire SQV.

~~5.1.4.~~5.1.3. The ~~Overall~~ PI or designated research team member takes the sponsor representative on a tour of the approved areas of the Cancer Center. The tour will include viewing the physical environment only; the sponsor representative will not have access to confidential patient information. Managers of the areas to be toured must be notified in advance to schedule the tour. Due to privacy concerns and ~~precautions for~~ /or safety issues, specialty laboratories and ~~/or safety issues, certain~~ patient areas may not be accessible to the sponsor representative.

~~5.1.5.~~5.1.4. If applicable, arrangements will be made for the sponsor representative to briefly meet with requested personnel, i.e. the Pharmacy or the ~~Overall~~ PI.

5.2. **Site Initiation Visit (SIV)**

5.2.1. A representative from ~~the lead~~each site will contact the sponsor ~~and research teams at all participating DF/HCC sites~~ to schedule and confirm a date and time for the SIV. A ~~separate~~single SIV may be ~~needed~~scheduled for ~~at each~~all participating DF/HCC ~~site~~sites when feasible.

5.2.2. Attendees ~~will~~must include the ~~Overall~~ PI and all pertinent research team members (as available).

~~5.2.3. The representative from the lead site will confirm key information, including but not limited to:~~

- ~~Approximate number of attendees from each site~~
- ~~Anticipated length of the presentation~~
- ~~Whether or not a pharmacy or clinical research lab visit, or time to review regulatory binders or supplies, will take place during the SIV~~

~~5.2.4. The representative from the lead site will obtain the SIV agenda from the sponsor representative and confirm whether the sponsor representative will supply copies of the protocol.~~

~~5.2.5. At the end of the SIV, the representative from the lead site will inform the sponsor representative whether or not all materials are on site and develop a plan to address any outstanding issues.~~

~~5.2.6.~~ Documentation confirming that the SIV is completed must be obtained from the sponsor representative and placed in with the essential regulatory documents. If not provided, a copy of the SIV attendance sheet must be requested.

~~5.2.7.~~5.2.3. Documentation of training is required for anyone unable to attend the SIV.

5.3. **Routine Monitoring Visits**

5.3.1. DF/HCC allows for a maximum of two clinical trial monitors per visit. Each monitoring visit will last no more than two days and must occur between the hours of 9 AM and 5 PM (unless an exception is made and other times are mutually agreed upon by the research team and monitor). Individual DF/HCC institutions may have additional requirements regarding on-site and remote monitoring specific to their location.

5.3.2. The monitor will request all visits at least four weeks prior to the visit date. The monitor will inform the study coordinator whether one or two monitors will attend the monitoring visit. The study coordinator schedules the visit according to his/her availability and the availability of space. The study coordinator and monitor will schedule additional monitoring visits every four weeks or greater (provided space is available) following the initial visit.

5.3.3. At least two weeks prior to each routine monitoring visit, the study coordinator will receive a Monitoring Confirmation detailing the date(s) of the monitoring visit; the name(s) of the monitor(s); the anticipated arrival time; and exactly what will be reviewed.

5.3.3.1. The confirmation must indicate which subjects and what cycles will be assessed; whether or not regulatory binders will be reviewed; what medical records are needed; and what appointments need to be made (i.e. pharmacy, ~~Overall~~ PI, research laboratory, clinical research center). If this information is not received, the study coordinator will request this information from the monitor prior to the visit.

5.3.4. During the visit, the study coordinator will provide the monitor with the requested paper or electronic case report forms (CRFs), medical records and research charts with all corresponding source documents as requested in the Monitoring Confirmation Letter. The study coordinator will also schedule designated times for all individuals requested in the Monitoring Confirmation Letter to meet with the monitor.

5.3.5. Research data must be submitted according to the protocol's data capture and monitoring plan. Any deviations or exceptions from the plan must be approved by the ~~Overall~~ PI.

5.3.6. After the visit, the monitor will provide a report containing the following: 1) what was reviewed; 2) what was collected; 3) any expectations that were not met; and 4) any outstanding issues that need to be addressed prior to the

next monitoring visit. If this information is not received, the study coordinator will request this information from the monitor.

5.3.7. Any significant issues or concerns regarding a monitor, a monitor's conduct while visiting DF/HCC, or a monitor's findings must be communicated in writing to the ~~Overall PI, Site Responsible Investigator (if applicable),~~PI, and the site's clinical trials office.

5.4. **Data Collection and Case Report Forms**

5.4.1. The Sponsor determines the most relevant method of data capture for the study and designs an appropriate data collection tool (e.g., paper CRF, electronic CRF) that accurately collects the specific data needed to test the hypotheses or answer the research questions.

5.4.2. The Sponsor provides the research team with the data collection tool(s) (e.g., blank CRFs or access to the electronic data capture system) and discusses the timeframe for data reporting to be followed.

5.4.3. When protocol modifications or corrections alter the CRFs, the Sponsor will modify the CRFs to accurately represent the protocol and distribute the revised CRFs to the participating research sites within a timely manner. If CRFs are revised and the Sponsor requests re-visiting completed subjects' data, additional funding may be required and time frames for completion negotiated.

5.4.4. No subjects will be accrued to a trial lacking an appropriate data collection method or to a trial utilizing outdated CRFs due to protocol amendments. In this case, trials may be subject to further action including temporary closure to accrual.

5.4.5. The ~~Overall~~ PI and designated research team members will adhere to the submission deadlines and compliance requirements set forth by the sponsor, as agreed in the contract.

5.4.6. For any type of data lock, the monitor must notify the study coordinator, in writing, at least four weeks prior of the exact date of the data lock. This notification must include the following details: the anticipated date of the data lock; which CRFs need to be completed by that date; the date all data needs to be received by the sponsor; the date the last query should be

received by the study coordinator; and the date the last query is required to be sent to the sponsor.

5.4.7. For Phase I trials only: In the event of a safety review or dose escalation decision where data is needed urgently, the study coordinator may submit to the sponsor the preliminary safety data that is required for informational purposes only. This data will be subject to routine monitoring. Queries based on unmonitored (i.e., unverified) data will be considered invalid and will not be resolved until the data has been monitored.

6. APPLICABLE REGULATIONS & GUIDELINES:

21 CFR 50 – Protection of Human Research Subjects
21 CFR 54 – Financial Disclosure by Clinical Investigators
21 CFR 56 – Institutional Review Boards
21 CFR 312 - Investigational New Drugs – Drugs for Human Use
21 CFR 812 - Investigational Device Exemptions
45 CFR 46 – Protection of Human Subjects
FDA Industry Guidelines and Information Sheets
FDA Compliance Policy Guidance Programs: 7348.809, 7348.810, and 7348.811

7. RELATED REFERENCES:

International Conference on Harmonisation – E6

8. RELATED RESOURCES:

DF/HCC Guidance on Investigator Interactions with Monitors