

Dana-Farber/Harvard Cancer Center Site Management Plan

1.0 Oversight Responsibilities of the Overall Principal Investigator and Site Principal Investigator

A system using an Overall Principal Investigator (Overall PI) and Site Responsible Investigator (Site PI), as described in the Dana-Farber/Harvard Cancer Center (DF/HCC) Guide to Human Research Activities, is utilized for the conduct of clinical trial(s). The Overall PI has the ultimate responsibility for the conduct of the clinical trial. Each participating institution has a designated Site PI, who is responsible for the conduct of the trial at that participating institution. The Site PI is responsible for collaborating with the Overall PI to ensure appropriate clinical conduct.

There will be one FDA Form 1572 form signed by the Overall PI. This FDA Form 1572 covers all participating DF/HCC clinical sites. The Site PIs are listed as sub-investigators on the FDA Form 1572.

All essential regulatory documentation is maintained by the Overall PI in a master file at their respective site and is communicated to the Site PIs and study staff as required. This includes all regulatory documents submitted to the Dana-Farber Cancer Institute (DFCI) Institutional Review Board (IRB). Each Non-Lead site maintains a limited subset of regulatory files necessary to conduct the study at their institution.

The DFCI IRB accepts electronic submissions for active clinical trials. The Overall PI is copied via email on all submissions for a given study. This enables the Overall PI to be aware of any and all submissions to the IRB, including SAEs and deviations that are generated at the participating sites. This also serves as acknowledgement of these submissions. Copies of all submissions generated at Non-Lead sites will be maintained at the site of origin per applicable DF/HCC Standard Operating Procedures. The Lead Site Study Coordinator is copied via email on all submissions to ensure that copies are filed in the master regulatory binder.

Additional periodic communication between the Lead Site and Non-Lead Sites are conducted including convened meetings, teleconferences or email distributions in which other protocol/research participant related issues can be reported. Documentation of the study communication is filed in all regulatory binders. Participation includes all appropriate research staff, including investigators, research nurses and study coordinators.

2.0 Institutional Review Board

The DFCI IRB is the IRB of record for human subject(s) research related to cancer for the five clinical institutions that comprise Dana-Farber/Harvard Cancer Center (Attachment 1). As previously noted, the Lead Site submits the majority of the regulatory documents. This includes continuing reviews, consent changes, protocol amendments, research team update forms, IDB amendments, etc. Some submissions, such as SAE reports and deviation/violation reports, are submitted to the IRB by the Non-Lead Site at which the event occurred. The responsible Site PI oversees the submission of these site-specific reports. All communication from the IRB is sent via email to the pertinent research staff, including investigators, study coordinators, and research nurses. This includes official approval documents, which are sent as attachments. Original stamped or signed copies of approval letters are not sent by the IRB. This is not a requirement of the FDA, and is not the policy of the DFCI IRB.

3.0 Study Oversight/ Dissemination of Study Safety Information

Study Oversight

The site of the Overall PI is designated as the Lead DF/HCC Site for the study. The Lead Site manages the overall coordination for the clinical trial. The Overall PI designates a study coordinator to aid in study logistics including coordination of study visits (e.g. pre-qualification and site initiation visits) and shipment of study supplies from sponsor to each site. The Lead Site is also responsible for overseeing patient recruitment at each participating DF/HCC institution to ensure the correct numbers of subjects are enrolled as agreed in the contract.

Regular communication between Lead Site and Non-Lead Sites ensures that contact information is up-to-date. There is frequent phone and email communication. The sites are aware that if there is a change in contact information the Lead Site must be notified.

Dissemination of Study Safety Information

At the time of the initial IRB application, the email distribution list for study specific correspondence from the IRB is generated by the Lead Site by submission of Co-Investigator/Research Staff forms. This list is updated with study staff changes as necessary by the submission of research team update/change of study staff forms.

IND Safety Reports

The Overall PI reviews all IND Safety Reports and determines whether or not they meet the DFCI IRB IND Reporting Policy for submission to the IRB. The Overall PI is responsible for submitting the applicable report(s) to the DFCI IRB as an Amendment. To ensure that safety information is properly disseminated, all study staff are copied via email on official IRB correspondence.

SAE Reports

Each individual site generates its own SAE reports for both the IRB and sponsor, if applicable (in accordance with procedures described in the protocol). Concurrent notification of the Overall PI is required as part of the electronic submission process as previously described. The IRB notifies all study staff via email when the SAE has been reviewed and attaches any documents that have been revised, such as the informed consent form, along with the IRB approval document.

4.0 Training of Site Study Staff

All new employees receive site-specific training as provided by each institution. Research staff are trained as appropriate for their protocol specific tasks.

Investigators Meeting and/or Site Initiation Visit (SIV), if required by sponsor

Investigators who were unable to attend the Investigator's Meeting and/or Site Initiation Visit (SIV) do attend meetings (as previously mentioned) where details of protocol eligibility, treatment schedule, toxicity management, etc. are discussed.

Study Coordinators involved in the study may attend the SIV and Investigator's Meeting and are responsible for training any other staff assisting them on the project as appropriate.

In-Service(s), if required

Infusion room nurses and pharmacy receive an in-service by the research nurse staff at which specifics of the protocol such as drug administration is discussed. Nurses and pharmacists who attend the in-service are required to sign an attendance sheet. This is coordinated by the research nurse and serves as documentation of training

The Clinical Trials Education Office (CTEO) provides general training for clinical research staff at all DF/HCC institutions. Sessions for new research staff are designed to provide an orientation as to how clinical trials are conducted at DF/HCC and give staff the opportunity to ask questions about their responsibilities. Ongoing education sessions for experienced staff focus on ethical issues in clinical research, barriers to day-to-day trial management and clarifications about how to apply regulations and guidelines to current practices.

5.0 Informed Consent Documents

The most recent approved version of the informed consent document is available on OncPro, and thus all consent forms must be printed out from OncPro to ensure the correct version is used. The date and time that a consent form is printed is noted at the top of the consent form. All clinical research staff are informed of this during their initial training. The IRB notifies all study staff via email when a new consent form is being posted on OncPro.

DF/HCC requires that participants in clinical trials be registered centrally through the Quality Assurance Office for Clinical Trials (QACT). As part of the registration process, study staff must fax the entire signed consent and completed eligibility checklist. The QACT Protocol Registrar reviews the faxed documents and if complete, registers the participant. When a participant is successfully registered the study team receives confirmation via email. If a participant is not properly registered, s/he can not receive protocol therapy.

Ensuring that a patient is consented and/or has been re-consented is the responsibility of the treating Investigator at each site. The research nurse and/or study coordinator keeps track of consent form updates and informs the treating physicians when participants are required to be notified or re-consented. At the time of consent form revisions, the Overall PI must inform the IRB if the changes may affect the subject's willingness to continue participation in the study. If this is true, the plan to notify participants (by documentation in medical record or by signing the new consent form) is stated on the amendment form. If a plan to notify participants is outlined on the amendment form, it is the responsibility of the Lead Site to ensure that this plan is carried out as stated. If no notification plan is indicated on the Amendment form the DFCI IRB will notify the Overall PI in writing if they have determined that the subjects must be notified and whether re-consenting by signing the updated consent form is required. The Lead Site is responsible for ensuring the Non-Lead Sites are aware of the need to re-consent.

6.0 Study Drug Storage/ Transport/ Dispensation

Maintenance of Drug Accountability Records

Drug inventory records are maintained by the research pharmacy at each of the sites utilizing the NCI Drug Accountability Form.

Handling of Used Vials and Unused Drug

The pharmacist or a pharmacy technician under the supervision of a pharmacist at each site will be responsible for handling the vials and drugs within the pharmacy.

Storage

BIDMC: All investigational agents are stored in a separate locked, limited-access research pharmacy facility. All unused bulk chemotherapy (antineoplastic/cytotoxic) waste, unless characterized as a non-hazardous pharmaceutical, cannot be destroyed by the current medical waste disposal company. This material will be returned to the study sponsor for destruction. Trace chemotherapy waste including sharps, syringes, IV tubing, BAS bottles, vials and other discarded contaminated items generated in the preparation and administration of cytotoxic antineoplastic drugs, will be accepted by the medical waste disposal company for destruction. BIDMC will only guarantee the storage of used chemotherapy vials for a period of two weeks. After that time, used chemotherapy vials will be placed in biohazard waste containers located in the pharmacy and be destroyed by the medical waste disposal company. Non-hazardous investigational agents will be either destroyed or will be returned to the sponsor for destruction depending on the sponsor's requirements.

DFCI: Investigational agents are stored in a locked room/satellite with restricted access. DFCI does not retain used vials per institute policy. Unused investigational agents from within the pharmacy are returned to the sponsor or destroyed onsite as per sponsor's directive. Used investigational agents from within the pharmacy, depending on the amount remaining in the vial, are destroyed according to DFCI guidelines for chemotherapy and hazardous waste. The pharmacy investigational drug storage area is monitored for temperature. Refrigerators and freezers have temperature monitoring/ recording devices.

MGH: All investigational products and supplies, as well as accountability records and patient information, will be maintained within the pharmacy. The pharmacy has a limited access key card system. Only pharmacy personnel have access to dispensing and storage areas. If non-pharmacy personnel require entry into the area for maintenance or auditing purposes, they are supervised at all times. The pharmacy is maintained at controlled room temperature as required by United States Pharmacopoeia Standards. The pharmacy also has proper refrigeration and freezer facilities for storage of drugs that require special storage conditions.

Drug Destruction Policy

BIDMC: See "Storage" section above for the used vial and unused drug policy.

DFCI: The drug destruction DFCI Standard Operating Procedure is on file. A copy will be provided if required.

MGH: All used investigational products are placed in a Chemotherapy Waste Container immediately after drug preparation and dispensation. Each container will then be sealed and stored with other containers of chemotherapy waste. At the end of each day, Environmental Services will remove the containers from the pharmacy to the building's loading dock for pickup by an outside vendor hired by MGH. All materials are then incinerated at an off site facility. Please refer to the MGH Standard Operating Procedure for further details.

Management of Drug Expiration Extension

Upon notification from the sponsor of any pending expiration dates:

BIDMC: Expired drug is maintained separately until it can be destroyed/sent back to the company.

DFCI: Any expired drug is sequestered from inventory and marked "Do Not Use" until it can be returned/destroyed or the expiration date is extended. Please ensure the Research Pharmacy's contact information is on file for such extension notifications.

MGH: Inventory is conducted on a monthly basis and at that time expiration dates and/or extension dates are recorded. Expired investigational product or supplies are removed from inventory and marked "Do Not Use"

or “Expired”. Extension notifications are recorded on inventory records and are kept on file as a permanent record. The research pharmacy returns or destroys investigational products once the appropriate party provides the proper disposition procedures.

Processes for Prevention of Errors in Drug Dispensation

All investigational drugs are marked with the DFCI IRB protocol number. Each patient is registered through the QACT before they can receive study drug. This registration is verified prior to dispensing.

Study Drug/Supply Shipment

Drug and study supplies (CRFs, Lab Kits, etc.) are shipped from the sponsor to the research pharmacy of each site.

7.0 Source Documents

BIDMC: Electronic records are the source of information. All labs, reports and clinician visits are posted in our Online Medical Record (OMR) system. This information is copied and stored in the research shadow chart, which is maintained by the study staff. Information relevant to the trial that is contained in the treatment chart (nursing notes, vital signs, orders, and medication administration records) is copied and placed in the research shadow file as well. In-patient and ER information not in OMR is obtained and the paper medical record copied and stored in the research shadow chart. All electronic notes must be signed by the author and PI as appropriate. While BIDMC does not provide access keys to monitors, the study coordinator will work with the monitor to ensure that the monitor has access to all relevant information.

MGH and DFCI: The electronic medical record system (Longitudinal Medical Record, LMR) is used in combination with a paper chart. Documents such as infusion flow sheets and doctor’s clinic notes are created in LMR and then printed and filed in the paper chart (research subject files). The research subject charts are available for review by the study sponsor for the purposes of monitoring the study. All electronic notes, labs, radiographic exams during the patient’s treatment are printed off of the online medical records and maintained in the subject research files.

8.0 Case Report Forms

The study coordinator responsible for the study at each site completes CRFs. Monitoring occurs at each individual site. Query resolution should be directed to the study coordinator at the site maintaining the CRF that generated the query. The PI at each DF/HCC institution (Overall PI or Site PI) are responsible for signing the CRF signature pages, if applicable, for that site.

9.0 Maintenance/Record Retention of Regulatory Files

The master regulatory file is maintained at the lead site. This binder contains all IRB submissions, approval, correspondence, the FDA Form 1572, all of the investigators’ CVs and medical licenses, all SAEs, all lab normals, the official screening and enrollment logs, etc. In short, all of the documents required to be in the regulatory binder are kept at the lead site. However, each participating site maintains a site-specific non-lead regulatory binder, which will contain the following documents:

- Any safety information sent to their site (e.g. IND safety reports, Dear Dr. Letters). Documentation of assessment of IND safety report will be kept at the Lead Site.
- Original approved Protocol, IRB Approval Memo, IRB Activation Memo

- Site Signature/Delegation of Authority Log
- Pertinent e-mail correspondence between sites
- Subject Identification Code List for that site
- Subject Screening/Enrollment logs for that site
- Any IRB communications generated by that site, i.e. SAE reports, deviations/violations

Study drug logs are maintained independently at the research pharmacies at each site and will be monitored individually.

The completion of study is defined as when the sponsor verifies that all data is up-to-date and correct (e.g. there are no outstanding queries, the final report has been approved by the IRB, and a formal study close out visit is completed). At that point, the documents are shipped to a long-term storage facility where they are kept for the period required per 21CFR312(c). Documents can be retrieved from the long-term storage facility within 24 hours if necessary.