DATA AND SAFETY MONITORING PLAN

DANA-FARBER/HARVARD CANCER CENTER

Version	Revision Date
6.0	November, 2020
5.1	September, 2017
5.0	April 20, 2016
4.0	June 15, 2013
3.0	July 31, 2012
2.0	November 1, 2011
1.0	Original Submission

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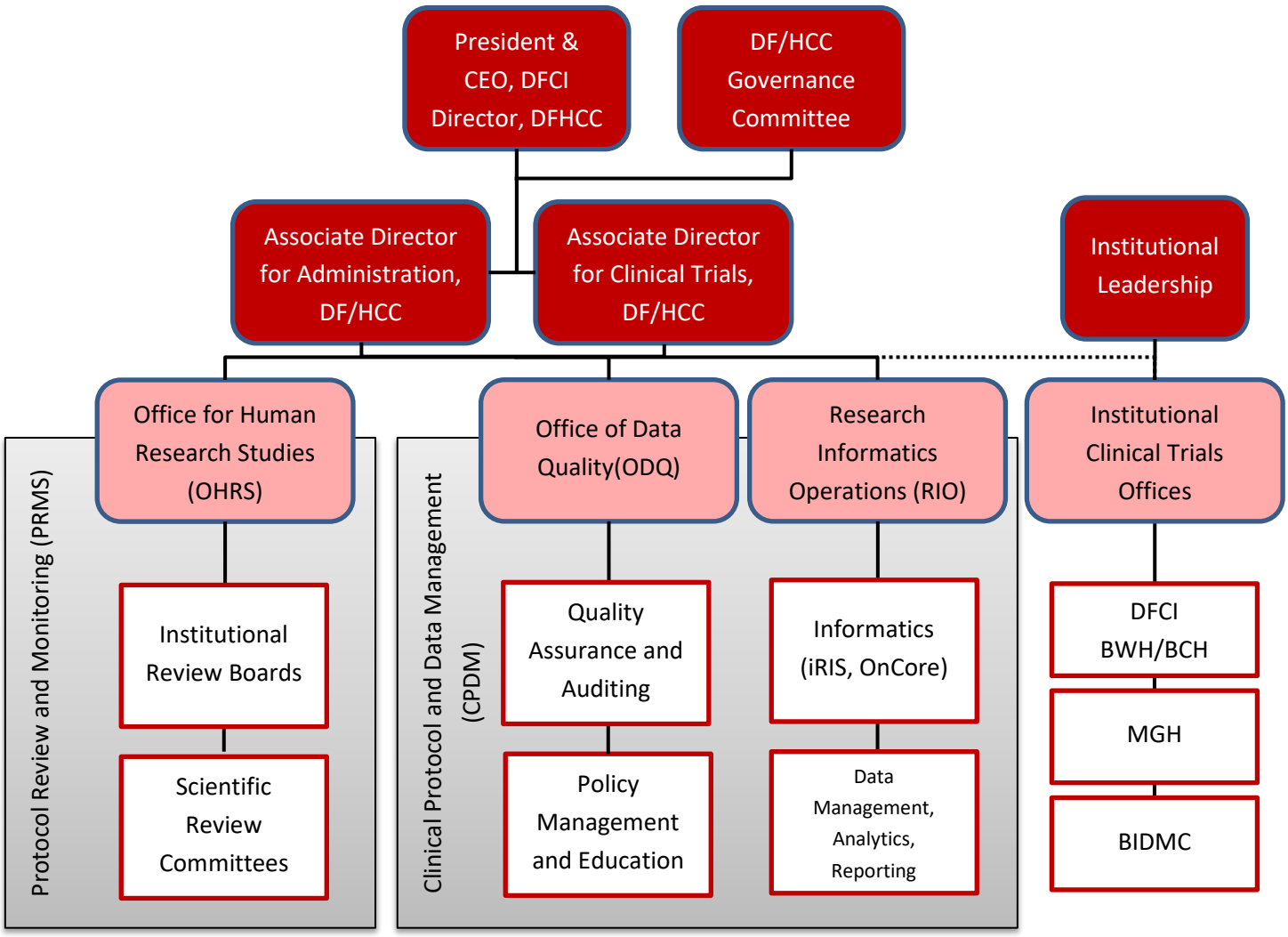
Table of Contents

1 INTRODUCTION

This document describes the institutional data and safety monitoring plan for cancer clinical trials that are performed under the umbrella of the Dana-Farber/Harvard Cancer Center (DF/HCC) by the five consortium institutions: Dana-Farber Cancer Institute (DFCI), Brigham and Women's Hospital (BWH), Massachusetts General Hospital (MGH), Boston Children's Hospital (BCH), and Beth Israel Deaconess Medical Center (BIDMC).

As a consortium type cancer center, DF/HCC has a unified clinical trials program and centralized clinical trials infrastructure that supports system-wide clinical trials activities. All oncology trials in DF/HCC go through a central protocol review and monitoring system (PRMS) managed by the Office for Human Research Studies (OHRS). In addition, the Clinical Protocol and Data Management (CPDM) is responsible for coordinating, facilitating, and reporting of DF/HCC cancer-related trials and ensuring that they are conducted in a consistent and cohesive manner across all institutions. The CPDM encompasses two offices, the Office of Data Quality (ODQ) and Research Informatics Operations (RIO). ODQ is responsible for clinical research quality assurance, clinical research education, and inter-institutional operations coordination. RIO provides clinical research informatics, data management, and clinical research analytics and reporting.



The consortium-wide committees that provide institutional oversight are the Scientific Review Committee (SRC), DFCI Institutional Review Board (IRB), Executive Committee for Consortium Clinical Research (ECCCR), Audit Committee, Data and Safety Monitoring Committee (DSMC), and Data and Safety Monitoring Board (DSMB). Individuals from DFCI, MGH, BWH, BCH and BIDMC and unaffiliated individuals serve as members on committees as appropriate.

2 COMMITTEE STRUCTURE

2.1 SCIENTIFIC REVIEW COMMITTEE (SRC)

As part of the PRMS, scientific review is required to assess scientific merit, feasibility and prioritization. This review is conducted by one of five DF/HCC Scientific Review Committees. For clinical trials, there are three adult SRCs and one pediatric SRC (PSRC) charged with reviewing all cancer related human subjects research. A fifth SRC reviews non-clinical human subject research. For protocols involving adult and pediatric subjects, the protocol will be

assigned to the pediatric committee. An SRC member with adult expertise provides representation for the adult component at the pediatric meeting.

Each committee is made up of members with the expertise necessary to make the required scientific decisions. Membership is comprised of physicians, physician-scientists, and biostatisticians. Ad hoc reviewers may also attend if deemed necessary by the Chairperson.

The OHRS provides administrative support and retains all documentation related to actions taken by the SRC and PSRC. All required documentation is centrally maintained in this office. The Director of OHRS, reports directly to the DFCI Senior Vice President for Cancer Center Administration who also serves as the DF/HCC Associate Director for Administration.

2.2 INSTITUTIONAL REVIEW BOARD (IRB)

All cancer relevant research conducted at any of the DF/HCC consortium institutions falls under the jurisdiction of the DFCI IRB, which by agreement serves as the IRB of record for all these studies, unless it is deemed appropriate to otherwise cede to a non-DF/HCC external IRB (e.g., the NCI CIRB). All the consortium institutions have Federal-wide Assurances with DHHS; and, all are AAHRPP accredited institutions. The DFCI has seven IRB panels (A, B, C, D, E, F, and G) registered with the US Department of Health and Human Services (DHHS), Office for Human Research Protections (OHRP).

IRB members typically serve for three-year terms; however, there are no term limits placed on length of service. Candidates for membership on the IRB may be identified by the individual institutions in their implementation of the DF/HCC policy requiring committee service; or, recommended by an IRB Chair, the OHRS Director and/or officials of the DF/HCC institutions that conduct human subject research reviewed by the DFCI IRB. Every effort is made to select personnel from different DF/HCC institutions and a variety of disciplines, which represent the types of research proposals submitted for review and approval. The IRBs comply with the membership requirements of DHHS regulations at 45 CFR 46.107 and FDA regulations at 21 CFR 56.107. The IRBs also comply with the written DFCI IRB policies and procedures for the Protection of Human Subjects in Research.

The OHRS administrates and supports the IRBs and provides all documentation for actions by the DFCI IRBs. All required regulatory documentation is centrally maintained in this office. The Director of OHRS reports directly to the DFCI VP of Research Operations under the DFCI Senior Vice President for Cancer Center Administration who also serves as the DF/HCC Associate Director for Administration.

2.3 EXECUTIVE COMMITTEE FOR CONSORTIUM CLINICAL RESEARCH (ECCCR)

OVERVIEW

The Executive Committee for Consortium Clinical Research (ECCCR) reviews clinical investigations activities, processes, and systems, as well as DF/HCC research policies, and provides inter-institutional representation and guidance at the highest level. While not required by NCI Guidelines, the ECCCR provides a regular forum for senior clinical research faculty and administrative leaders across the DF/HCC member institutions to discuss and resolve system-wide issues related to the conduct and support of clinical trials within DF/HCC. It also offers the critical

opportunity to synthesize information and identify global issues related to the Data Safety Monitoring Plan (DSMP) that require senior level decision-making.

While separate and distinct from the PRMS and CPDM processes, the ECCCR galvanizes the efforts of the CPDM and PRMS. The ECCCR serves as an umbrella entity, providing a forum for senior leaders to review reports, activities and trends, including those related to the DSMP. The ECCCR's goal is to synthesize this information to identify issues, trends and opportunities for improving the overall clinical investigations program and relevant operations, processes and infrastructure. Importantly, the representatives on this committee have the designated level of authority within DF/HCC and their affiliated organization to make decisions and to effect change.

The ECCCR is in a unique position to identify trends and issues that may not be immediately obvious to committees that are necessarily more focused in purpose. The ECCCR therefore plays a central role in detecting problems, proposing solutions, and communicating these concerns directly to the Center Director, Executive Committee, Administration, SRC and IRB leaders, and senior representatives from DF/HCC member institutions, as appropriate. Timely resolution of issues is assured by the fact that the leaders from each of these critical bodies, as well as those responsible for clinical trials operations, are also members of ECCCR.

The ECCCR advises the Center Director and Executive Committee regarding the various systems and processes related to the conduct of DF/HCC clinical trials. These processes and systems include, but are not limited to:

- System-wide, protocol-specific, or PI-specific issues that impact the appropriate conduct of clinical trials
- Organizational capabilities and resources related to clinical trials
- General issues related to trial design that impact the effective conduct of trials
- Inter-institutional policies and practices that impact the conduct of clinical trials
- Concerns that arise from clinical trial review, auditing and monitoring processes
- Issues that individual institutions have regarding the clinical investigations program
- Operational issues that require senior faculty input and institutional consideration on clinical trials issues

Depending on the circumstances, ECCCR may be able to resolve an issue directly, request input from other committees or senior leadership, or refer issues to other DF/HCC individuals or bodies, such as the Center Director, Executive Committee, Clinical Sciences Executive Committee, Administration, and Associate Director for Clinical Trials. ECCCR may identify issues that require implementation or follow-up by one of the DF/HCC institutions. The ECCCR Chair, with the advice of the Associate Director for Administration and, as needed, the Center Director, determines the best possible process for conveying and resolving these concerns.

Throughout the year, issues requiring the prompt attention of the Center Director or Executive Committee are communicated, as needed. Annually, the ECCCR Chair and Associate Director Clinical Trials is invited to provide a report to the Center Director and Executive Committee. The report covers the key issues and actions of the committee during the past year, as well as the actions taken by other committees and groups because of ECCCR efforts.

MEMBERSHIP

The Center Director, or designee, appoints all ECCCR members, including the ECCCR Chair. Members are appointed for three years and may be reappointed with the concurrence of the Center Director. At a minimum, members should include: Associate Director for Administration, who also serves as SVP-CA for DFCI; Associate Director for Clinical Trials, DF/HCC; faculty leaders in clinical trials (preferably faculty who are also on the Executive Committee) and administrative representatives from the DF/HCC member institutions.

MEETING STRUCTURE

Generally, the ECCCR will meet once a month during the academic year. There is no set quorum for this Committee. However, should the Chair determine that the number or composition of the attendees is not appropriate relative to the issue; s/he may defer the discussion until the next meeting.

The ECCCR Chair, the Associate Director for Clinical Trials, and Associate Director for Administration serve as an ad hoc executive committee if there is an immediate issue that needs to be addressed before an emergency meeting can be convened.

INTER-INSTITUTIONAL REPRESENTATION

Because of its inter-institutional composition, ECCCR serves as a face-to-face forum in which PI-specific or system-wide clinical trials issues can be discussed and resolved. Each DF/HCC institution is responsible for identifying a senior faculty person at the institution to whom ECCCR can communicate clinical trials-related concerns. This individual serves as a member of ECCCR and is accountable for keeping the leadership and Board of Trustees at their respective institution informed about relevant DF/HCC clinical trials issues. The senior faculty representative is responsible for reporting back to the ECCCR regarding actions taken at each institution in response to ECCCR-identified matters. Each institution is also responsible for identifying the appropriate administrator at the institution to whom ECCCR can communicate clinical trials-related concerns.

ECCCR institutional representatives are responsible for following up on issues relevant to their institution that are discussed at ECCCR meetings or brought to their attention. They are responsible for keeping institutional and/or DF/HCC leadership, as appropriate, apprised of the status and resolution of such matters.

2.4 CLINICAL RESEARCH OPERATIONS SUB-COMMITTEE (CLINOPS)

The Clinical Research Operations Sub-Committee (CLINOPS), a sub-committee of the ECCCR, is a component of the CPDM. The purpose of CLINOPS is to review DF/HCC clinical trials operations, facilitate inter-institutional communication, resolve CLINOPS-identified clinical trial issues, and develop and/or revise DF/HCC policies and operations for human subject research. New and revised policies and operations developed by CLINOPS referred to ECCCR for additional comment and review.

There are three working groups that report to CLINOPS. The Nursing Working Group, Pharmacy Working Group, and Education Working Group each maintain representatives from across the consortium and focus on operational issues specific to their scope.

Members include key representatives with clinical trials responsibilities from DF/HCC member institutions, including, but not limited to, such areas as nursing, pharmacy, OHRS, ODQ and RIO. Minutes of the CLINOPS meetings are maintained by the Office of Data Quality (ODQ).

2.5 AUDIT COMMITTEE

The Audit Committee oversees the review of the DF/HCC Internal Audit Program, provides clinical input for the audited protocols and identifies any needed DF/HCC system changes brought to light through the internal audits. The Audit Committee meets monthly to ensure timely oversight of internal and external audits. ODQ manages the administrative tasks of the Audit Committee.

DF/HCC Administrative Leadership appoints Audit Committee members for a minimum of three years. Membership includes representation from the DF/HCC institutions, biostatistics, pharmacy, nursing, the Office for Human Research Studies (OHRS) and the Office of Data Quality (ODQ). A quorum consists of a minimum of six of the voting members, including at least one physician.

2.6 DATA AND SAFETY MONITORING COMMITTEE (DSMC)

OVERVIEW

The DF/HCC Data and Safety Monitoring Committee (DSMC) reviews high-risk pilot, Phase I and Phase II protocols initiated and conducted by DF/HCC investigators. High-risk protocols include but are not limited to:

- DF/HCC investigator-sponsored interventional clinical trials, which includes but not limited to DF/HCC multi-center trials, investigator held IND/IDE trials
- First in human and/or pediatric clinical trials that do not have an established DSMC
- Gene transfer protocols which 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 DSMC as determined by the ECCCR, SRC, and IRB

The DSMC is tasked with providing ongoing monitoring of safety, data compliance, and overall study progress. The DSMC advises the IRB and/or DF/HCC Associate Directors of any recommended actions, and reports into the ECCCR.

MEMBERSHIP

Consisting of internal DF/HCC faculty and staff, the committee membership is large enough to ensure meetings occur monthly and/or more regularly if required. DF/HCC Leadership appoints the voting membership of the DSMC. Voting members include physicians, statisticians, other scientists, based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of clinical trials methodology.

The following members have been selected for the DF/HCC DSMC:

- 3 Medical Oncologists (1 acts as Chair)
- 1 Pediatric Oncologist (may be one of the above)
- 1 ad hoc Physician as needed (Radiation Oncologist, Surgeon)
- 1 Biostatistician

- 1 Nurse
- 1 Pharmacist

A representative from ODQ serves as a non-voting member and provides administrative support.

2.7 DATA AND SAFETY MONITORING BOARD (DSMB)

OVERVIEW

The DF/HCC Data and Safety Monitoring Board (DSMB) reviews DF/HCC investigator-sponsored protocols or large randomized protocols that otherwise do not have an independent DSMB assigned and do not fall under the purview of the DF/HCC DSMC. ODQ provides administrative support and coordinates the meetings.

The DSMB is tasked with:

- Reviewing the research protocol(s) and plans for the data and safety monitoring.
- Evaluating study summary data to determine protocol progress and whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- Reviewing reports of related studies to determine whether new information means the monitored study needs to be changed or terminated.
- Reviewing major proposed modifications to the study prior to their implementation (e.g. termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).

The DSMB advises the IRB and/or DF/HCC Associate Directors of any recommended actions, and reports into the ECCCR.

MEMBERSHIP

DF/HCC Leadership appoints the voting membership of the DSMB. Voting members include physicians, statisticians, and other scientists, based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of clinical trials methodology. The minimum composition of the DSMB is maintained as follows:

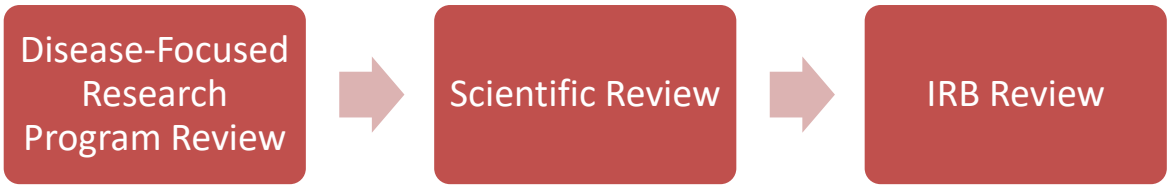
- Chair, Medical Oncologist (External, outside DF/HCC)
- Medical Oncologist (External, outside DF/HCC)
- Medical Oncologist (DF/HCC)
- Pediatric Oncologist (may be any of the above)
- Other Scientist (radiologist or surgeon –within DF/HCC)
- Statistician (External, outside DF/HCC)
- Ad Hoc membership (if special expertise is needed)

Voting members may be from within or outside the institution, but a majority should not be affiliated with the institution. Voting members should not be directly involved with the conceptual design or analysis of the trial. A representative from the Department of Biostatistics and Computational Biology serves ex-officio as a non-voting member of the DSMB.

Each member of the DSMB must sign a confidentiality agreement. DSMB members will be expected to follow the Harvard Medical School guidelines for disclosing conflicts of interest and will sign a statement agreeing to that policy at every meeting.

3 OVERSIGHT OF TRIALS PRE-ACTIVATION

Prior to activation of a new clinical trial, all trials go through the PRMS multi-step review process to assess a protocol's feasibility, resource requirements, novelty, scientific importance, risk, and safety. Oversight is provided by the disease-focused research program, the SRC, and the IRB.



Additional review and approval is required for all multi-center trials as described in Section 3.4.

3.1 DISEASE-FOCUSED RESEARCH PROGRAM REVIEW

Disease-focused Research Programs include representation from all participating institutions. They review and approve all proposed protocols for feasibility and determine priority within the Disease Program. During this process, the resource requirements and logistical needs of the protocol are evaluated to ensure the protocol can be conducted properly and safely by each participating research program.

3.2 SCIENTIFIC REVIEW

As part of the PRMS, scientific review is required to assess scientific merit, feasibility and prioritization. During the review process, the SRC or PSRC members consider the novelty and importance of the research questions, the feasibility of the research plan, the capability of the research team to conduct the trial in a timely fashion, and whether the protocol is competing with other protocols already enrolling.

Scientific review occurs prior to IRB review. New protocols will not be sent to the DFCI IRB until a determination has been made that the investigators have adequately responded to all conditions for scientific review approval.

3.3 IRB REVIEW

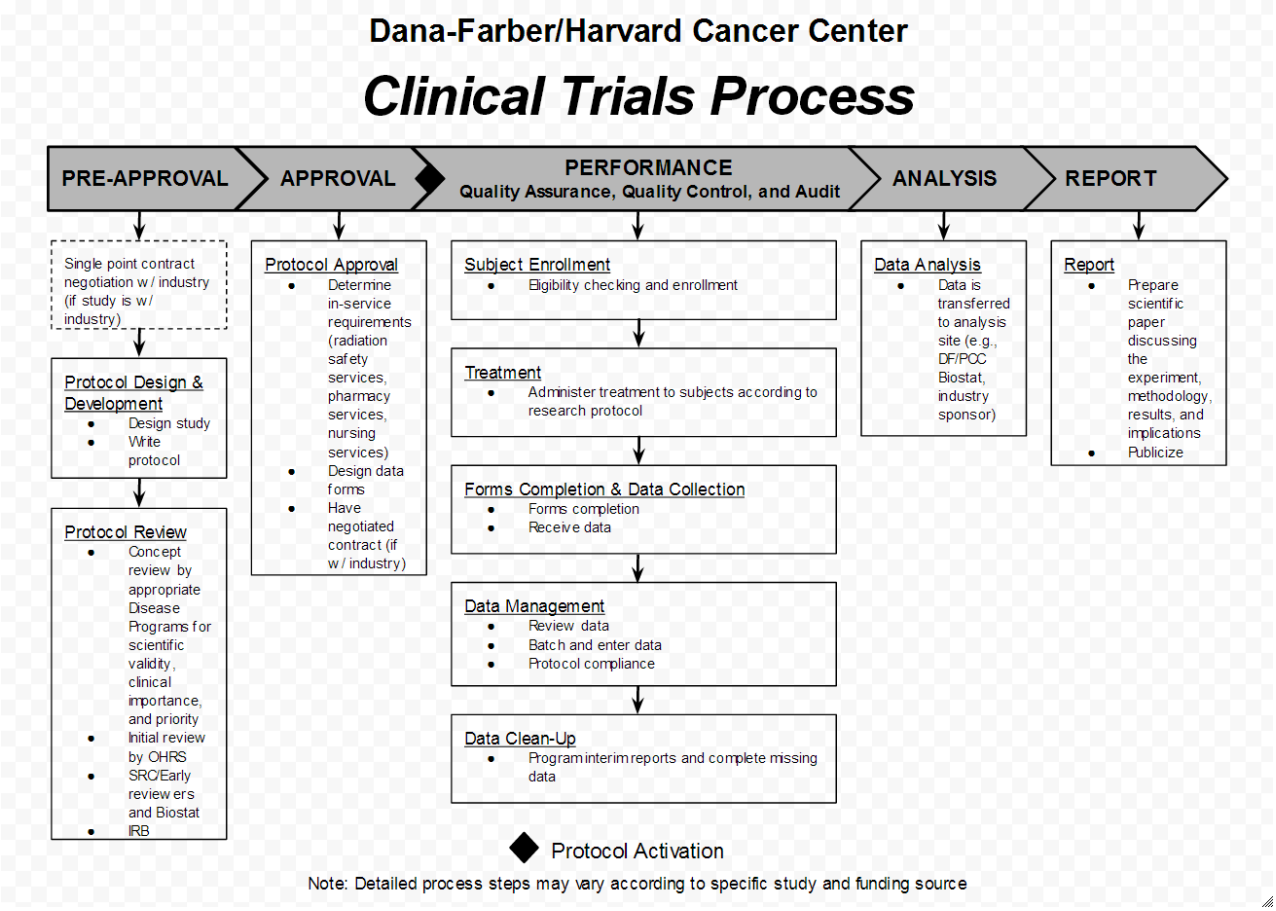
The DFCI IRBs review research involving human subjects and have the authority to approve, require modifications in, or disapprove all research activities, including proposed changes in previously approved human subject research. No official or committee of a DF/HCC institution may permit the conduct of human subject research that has not been approved by an IRB.

3.4 MULTI-CENTER TRIAL REVIEW

DF/HCC member institutions are required to conduct a separate review of all new, investigator-sponsored, multi-center trials. This review occurs prior to IRB review and approval and ensures that the sponsor-investigator has the appropriate resources to conduct the multi-center trial and will have appropriate oversight of trial conduct at all sites.

4 OVERSIGHT OF TRIALS POST-ACTIVATION

There is ongoing monitoring throughout the life of the protocol via PRMS review, auditing, required reporting, and data and safety monitoring.



During the conduct of a trial, oversight is provided through close coordination between multiple oversight committees and departments. The oversight committees may request a corrective action plan based on observed and/or reported deficiencies and non-compliance in trial management. If an issue could potentially affect subject safety, the IRB is notified. The Committees may also request follow-up information on AEs/SAEs and make recommendations regarding the status of the study or consent form modifications if there are concerns about safety or quality.

4.1 SCIENTIFIC REVIEW

The Scientific Review Committee (SRC) is responsible for monitoring the accrual and evaluating the scientific merit of each interventional clinical research trial. The committee utilizes a risk-based methodology for this monitoring process.

Monitoring of zero and slow-accruing trials maximizes subject contributions by minimizing the likelihood that research will fail to complete its objectives. This also promotes efficient use of resources and maximizes the likelihood that research supported by DF/HCC Institutions will be completed, reported, and published. All active protocols are reviewed for slow or inadequate accrual, based on DF/HCC Operation COM-OP-2, which defines specific parameters for accrual rates. The SRC has the authority to close trials due to slow accrual.

Monitoring of rapidly accruing trials identifies research that requires close monitoring to ensure adequate resources, prospective data collection and appropriate safety review.

Evaluation of the scientific progress of the trial, and how that fits into overall progress in that specific area of research, is important to ensure that the trial is continuing to address an important scientific question.

4.2 IRB REVIEW

The IRB has the authority to observe and/or monitor DF/HCC research to whatever extent they consider necessary to protect human subjects. They also have the authority to suspend or terminate research for serious or continuing non-compliance with the Common Rule, DHHS regulations, and FDA regulations, or its own findings, determinations, and requirements.

All DF/HCC cancer related trials fall under the jurisdiction of the DFCI IRB, unless there is an established reliance agreement designating an external IRB as the IRB of record.

DFCI IRB Panels routinely review Continuing Reviews, Amendments, Other Events (including deviations, violations and exceptions), Adverse Event (AE) reports and unanticipated problem reports. These committees perform a detailed review of all submissions and associated documents. If additional information is needed to complete the review and make a determination the committee will query the PI. At the completion of the review, the IRB is authorized to take any action deemed necessary to ensure subject safety, protocol compliance and data integrity. The IRB's determination is binding on all participating institutions

CONTINUING REVIEW

Continuing Review occurs at least annually for all protocols under the jurisdiction of the DFCI IRB except for qualifying, non-FDA regulated, minimal risk studies. For clinical trials, the review focuses on the risks, benefits, adverse event reports, other events (including deviations, violations, exceptions and unanticipated problems), the overall scientific progress of the research, and ensures the informed consent is accurate and up to date.

AMENDMENTS

Proposed amendments to previously approved research are reviewed by the SRC (if applicable), the IRB, and once approved are sent for activation (as required). The IRB determines when it is necessary to inform subjects of any new findings that reveal additional risk or information that may alter their willingness to participate in the research.

The most recent version of the protocol, consent document, eligibility checklist, and disease program priority lists are maintained electronically by the ODQ using the Oncology Protocol System (OncPro) which is available to all investigators and research staff at DFCI, BWH, MGH, BCH, BIDMC, and authorized Dana-Farber/Partners Cancer Care (DF/PCC) Network Affiliates. The Sponsor-Investigator or designated research team member is responsible for keeping participating sites that do not have access to OncPro updated on changes to research related documents.

STUDY CLOSURES

All temporary or permanent closure determinations made by the IRB or DF/HCC due to non-compliance or safety concerns will be reported by the DF/HCC Principal Investigator in conjunction with their grant manager to the NCI Grant Program Director on NCI-sponsored clinical trials (non-cooperative group studies). These closures will be reported to the NCI Program Director within 10 working days of the determination. OHRS is responsible for reporting suspensions in IRB approval to the appropriate regulatory agency when required.

4.3 DSMC REVIEW

The Scientific Review Committees (SRC and PSRC), Institutional Review Board (IRB), and/or Office of Data Quality (ODQ) will identify high-risk protocols to be reviewed by the DSMC. An initial review by the DSMC is triggered based on the first subject accrual to a protocol. DSMC reviews continue until the DSMC feels there are no subject safety concerns that require further monitoring.

MEETING STRUCTURE

The DSMC meets monthly to review toxicity, data submission compliance and accrual. Protocols are reviewed, on average, every six months. The DSMC may choose to increase or decrease the frequency based on the protocol status, accrual rate, and review of ongoing safety indicators. 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.

The DSMC requests information from the PI, study team, and the Office of Data Quality (ODQ) to facilitate review. This information includes up-to-date accrual, current dose level information, dose-limiting toxicity information, all grade 2 or higher unexpected and related adverse events, and participant deaths. Other information may be requested for multi-center trials or as requested by the committee. All trial and participant information remain confidential.

DSMC reviewers assigned to each protocol receive the requested information in advance. During the meeting, the assigned reviewer presents the trial, raises any concerns for discussion, and makes recommendations to the committee as to the frequency of review. DSMC meeting minutes are maintained by ODQ.

MEETING OUTCOME

Following each DSMC meeting, the committee notifies the PI and study team of the review outcome. This may include requests for additional information, requests for clarification, and the frequency of future DSMC reviews. A summary of each DSMC meeting is provided to the IRB chairs.

The PI and study team are required to respond to DSMC requests and recommendations expeditiously. When requested by the DSMC, the PI will respond in writing, and the DSMC will review the response at the next meeting. In cases where immediate action is needed to ensure subject safety, the IRB is empowered to suspend or close the study. Alternatively, concerns may be escalated to the DF/HCC Associate Directors.

4.4 DSMB REVIEW

The Scientific Review Committees (SRC and PSRC), Institutional Review Board (IRB), and/or the Office of Data Quality (ODQ) will identify protocols to be reviewed by the Data and Safety Monitoring Board (DSMB). The DSMB membership includes both voting and non-voting members. There are five permanent voting members of the DSMB, at least three of who come from institutions outside the DF/HCC. Voting members include physicians, statisticians, other scientists, based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of clinical trial methodology.

These trials will remain under the DSMB review until either the last enrollment occurs, or until the DSMB feels there are no subject safety concerns that require further monitoring. The DSMB will determine the frequency of continued review on a study-by-study basis.

MEETING STRUCTURE

The DSMB meets at least semi-annually depending on the nature and volume of the trials being monitored. Each meeting has three parts:

(1) An open session in which members of the trial team, including the statistician, may be present, at the request of the DSMB, to review the conduct of the trial and to answer questions from members of the DSMB. The focus of this open session may be on accrual, protocol compliance, and general toxicity issues. Outcome results must not be discussed during this session.

(2) A closed session of the DSMB is be held to allow discussion of the general conduct of the trial and all outcome results, including toxicities, and adverse events, develop recommendations and take necessary votes.

(3) A summary executive session follows to summarize and evaluate the overall meeting, and to plan the next meeting. The meeting may occur by conference call if necessary.

The DF/HCC expects that the DSMB will make decisions that are consistent with the intent of the design of a protocol and in the best interests of the study participants. In some instances, the DSMB may recommend changes to the design of a protocol, the timing of data collection or the details of an analysis because the assumptions made in the original design need modification, or because information external to the study suggests that revision is necessary. The deliberations of the DSMB should not be influenced by special interests of either the study team or the protocol sponsor.

MEETING OUTCOME

Following each DSMB meeting, the committee provides the study team with written information concerning findings for the trial related to cumulative toxicities observed and any relevant recommendations related to continuing, changing or terminating the trial. The DSMB also provides a summary of the board findings to the IRB chairs, and the Principal Investigator.

Outcome data for protocols still enrolling subjects are considered confidential and are not to be discussed outside the DSMB meetings. Any special release of this data should be approved by the DSMB. In instances where the DSMB recommends changes to the design of a study (including early stopping of enrollment because of the results of an interim analysis or changes in one or more of the treatments), the DSMB will provide in writing to the protocol PI a rationale for these recommendations.

When requested by the DSMB, the protocol PI will respond in writing to the DSMB and IRB detailing the actions taken regarding the recommendations and the reasons for those decisions. The study team is required to implement recommendations from the DSMB expeditiously. In cases where there is disagreement between the DSMB and the protocol PI, the IRB can adjudicate.

When the DSMB recommends accrual suspension because of subject safety concerns, the IRB is responsible for ensuring that the study is closed as soon as possible, but no longer than 24 hours after receiving the recommendation. In cases where an immediate action is necessary, based upon the severity of subject safety issues, the IRB is empowered to suspend or close the study. In less urgent situations, the IRB may confer with the Chair of Scientific Review Committee as well as with the DF/HCC Associate Directors, Clinical Trials Operations as to the most appropriate steps to implement the DSMB's recommendations.

In cases where the DSMB recommendation does not involve trial closure for subject safety, the IRB may decide to place the DSMB recommendation on the IRB agenda for a more complete discussion. The DSMB recommendation may also be referred to the Scientific Review Committee (SRC) if it involves accrual or scientific design issues that are not sufficient to recommend study closure, but sufficient to warrant a more in-depth evaluation. For administrative management, all communications to the Chairs of the IRB or SRC will be copied to the Senior Director of the Office for Human Research Studies.

4.5 DATA QUALITY

The Office of Data Quality (ODQ) is responsible for ensuring the integrity and timely submission of data for investigator-sponsored therapeutic trials. ODQ reviews clinical trial data to identify missing, illogical or ambiguous data, and to ensure timely data entry. ODQ will create data queries to request clarification or additional data entry and perform ongoing data cleaning. In addition, reports of missing data are available to the study team and PI on a regular basis.

Problems with obtaining data or data quality are referred to the trial monitor, auditing program or to the DSMC, depending on the severity of the circumstances. Problems with suspected misconduct are reported to the DF/HCC Associate Director for Administration and DF/HCC Associate Director for Clinical Trials.

4.6 PHARMACY AND NURSING

The DF/HCC research pharmacy representatives from DFCI, BWH, MGH, BCH, and BIDMC meet regularly in the Pharmacy Working Group. Similarly, institutional nursing representatives meet regularly in the Nursing Working Group. Each working group appoints a rotating representative to represent Pharmacy and Nursing at the Clinical

Trials Operations Committee (CLINOPS). The research pharmacists and research nurses report to their institutional directors and are represented on the IRB, CLINOPS, Audit Committee and DSMC.

All investigational drugs are marked with the DF/HCC protocol number. Subjects must be registered in the OnCore Clinical Trials Management System before they can receive study drug. The research pharmacy checks that a participant is formally enrolled on the research protocol before dispensing investigational drugs. In addition, for studies with dose escalation, the research pharmacy ensures that the subject is registered to the appropriate dose level before dispensing investigational drug.

4.7 SITE MONITORING

OVERVIEW

Every principal investigator, and the research staff delegated to assist that investigator in the conduct of research, has a responsibility to monitor the safety, conduct and progress of each research study. The protocol sponsor is additionally responsible for developing a monitoring and oversight plan appropriate to the risk of the trial. For investigator-sponsored trials, the Sponsor-Investigator is responsible for describing the monitoring plan. The DF/HCC Coordinating Center, and a designated trained monitor, as applicable, will implement monitoring activities to ensure that all sites are complying with regulatory and protocol requirements, data quality, and subject safety.

A risk-based approach is used to determine the appropriate level of monitoring. This includes considering the complexity of the study design, study endpoints, clinical complexity, study population, geography, experience of the participating investigators, experience of the sponsor in conducting these types of trials, data capture requirements, Known safety profile of the investigational product, and stage of the study. Studies are considered higher risk when a DF/HCC investigator holds the IND/IDE, DF/HCC is manufacturing the study agent, and/or when external institutions are participating on the trial (i.e., multi-center trials).

MONITORING ACTIVITIES

Designated monitors may conduct monitoring visits to ensure that participating sites' clinical investigators and study team members are compliant with the protocol, regulations and institutional polices; that data are of high quality and integrity; and that the facilities and staffing are adequate for continued participation in the study. The participating sites may be required to submit source documents to the Coordinating Center for remote monitoring. In addition, the participating site may be subject to on-site monitoring. Many trials include a combination of remote and on-site monitoring.

Monitoring practices may include, but are not limited to, source verification of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration / treatment, regulatory records, protocol deviations, pharmacy records, response assessments, and data management.

Following each monitoring visit, the monitor will communicate findings and any additional requests in a follow-up letter sent to the participating site's Principal Investigator. The monitor will also complete a monitoring report to

document the interim monitoring visit and provide it to the Protocol Chair and sponsor (the protocol chair serves as the sponsor for investigator-sponsored trials).

CLOSE-OUT MONITORING ASSESSMENTS

Closeout monitoring is usually conducted when all participants have completed the study, including treatment and follow-up assessments. At the Closeout monitoring assessment, the monitor is responsible for ensuring that the investigator conducted the study according to the protocol and in compliance with Good Clinical Practices and federal and state laws and regulations. The monitor will also ensure that the investigator is aware of his/her continued obligations. The Closeout assessment visit is to finalize all the necessary procedures to conclude the clinical investigation at a specific investigator site.

ESCALATION

Monitors are required to report any observed, suspected, or apparent research nonconformities to the Protocol Chair. In turn, the Protocol Chair communicates this information to the IRB of record, as applicable. The Protocol Chair may also notify ODQ to request an audit of a trial, site, or investigator. Further inquiries or investigations into the event may be needed and the outcome of these findings may result in increased monitoring, a for-cause audit, or early closure of the trial.

4.8 AUDITING

OVERVIEW

All research conducted at DF/HCC participating institution are subject to internal audit, including those protocols sponsored by NCI, pharmaceutical industry or other sponsors. All auditing activities are managed through ODQ to minimize the potential for institutional bias or conflict of interest inherent between investigators and audit functions within the same institution. The auditing staff report to the Data & Safety Monitoring Manager within ODQ.

The goals of the auditing process are:

- To ensure and confirm ongoing protocol compliance in accordance with DF/HCC guidelines, policies and operations, and US federal regulations.
- To educate the clinical research staff and promote greater awareness and understanding of policies, operations and objectives, and to increase efficiency and consistency in the conduct of clinical trials at DF/HCC.
- To identify areas where systemic process improvement in the DF/HCC policies and operations is needed to ensure compliance and enhance participant safety.

AUDIT PROCESS

The ODQ Data & Safety Monitoring Manager (DSMM) uses a programmed algorithm in OnCore to select protocols for routine audit. The algorithm assigns a ranking score to each study and prioritizes protocols for audit using several factors, including: DF/HCC investigator holds an IND/IDE, DF/HCC investigator-sponsored research project, external centers/sites are participating, rapidly accruing, new investigator or time since the investigator was last audited, and clinical trial phase. The DSMM also considers the disease program leading the protocol to ensure all programs are regularly included in routine audits. The Principal Investigator, designated study staff and institutional clinical trials offices are notified and provided with the following information:

- A letter listing the information that will be audited and scheduling.
- A list of study participants to be audited.
- A copy of the DF/HCC operation AUD-OP-1: Internal Auditing Procedures

The auditor will pre-select five to six participants to audit from a protocol. Unannounced participants may be selected at the time of the audit dependent on accrual. Participant selection is impartial; however, the auditor will consider the distribution of participants enrolled at affiliated sites and regarding the trail design, i.e. what treatment arms are participants assigned.

During the audit a thorough review of all study regulatory documentation is performed. The auditor will conduct a review of all protocol specific participant records as well as patient medical record used in support of trial participation. The selected participants' records, protocol regulatory documents and associated pharmacy records will be reviewed. During an audit, physicians and/or research staff are available to assist the auditor as needed.

Upon completion of the audit, an exit interview will be conducted by the auditor with the PI and the study staff. During the exit interview, the auditor will summarize their preliminary findings and the investigator and study team are given the opportunity to ask questions and help clarify any issues presented.

The Auditor will prepare and provide a written final audit report to the PI will be asked to sign acceptance of the audit report and reply with a corrective action plans as indicated by the findings.
The AUD-*OP-1: Internal Auditing Procedures resource* describes the audit process in detail and is readily available online on the DF/HCC website.

PROCESS AUDITS & RISK ASSESSMENT PROCESS

In addition to routine full scope audits, ODQ conducts Process Audits to focus on a specific area of study conduct, e.g., Informed Consent, Adverse Events reporting, or Delegation of Authority. A Process Audit may be protocol specific or an assessment performed within a disease group or across the Consortium membership. Process Audits are performed at the request of a Disease Program, IRB, or other DF/HCC or institutional oversight committee.

ESCALATION

The Audit Committee reviews audit results from internal and external audits to ensure that DF/HCC is aware of audit activity and findings. The Audit Committee will determine if follow-up action is necessary and may refer any problems to the appropriate oversight committee(s), including the SRC, IRB and ECCCR. The Audit Committee provides a monthly summary report to the IRB Chairs of the audits reviewed, the ratings given, and any issues identified at the last meeting.

If an audit is rated as "Unacceptable", the Data & Safety Monitoring Manager (DSMM) will notify the voting members of the Audit Committee, the DF/HCC Associate Director for Clinical Trials and the DF/HCC Associate Director for Administration of the violations within 48 hours of the exit interview. The notified members review the major violations and inform the DSMM if they agree with the "Unacceptable" evaluation within 24 hours. If the majority votes for the "Unacceptable" rating, a formal standardized letter from the Chair of the DF/HCC Audit Committee to the PI and PI's Division Chief will accompany the final audit report. This formal letter, sent within 24 hours of the majority vote, will alert the PI of the Audit Committee's agreement with the audit rating and will instruct the PI to prepare a written response to the major violations outlined in the final audit report within five working days.

If during an audit, a subject safety risk is discovered, the DSMM will notify the voting members of the Audit Committee and the DF/HCC Associate Director for Clinical Trials and the DF/HCC Associate Director for Administration of the violations immediately. The members must review the violations and determine an action plan by consensus within 24 hours. In addition, the DFCI Quality Improvement, Risk Management and Patient Safety Officers will be notified of any subject safety risks discovered. The Institutional Officials will be responsible for contacting their counterparts at collaborating institutions if applicable.

The DF/HCC Audit Committee has the opportunity at this point to take immediate action, including suspension of the trial and/or recommendation of closure to the IRB, if deemed necessary. Immediate action by the Audit Committee would take place in the event of suspected subject safety risks, research fraud, or an extremely problematic audit.

If protocol suspension were deemed necessary, the Chair of the DF/HCC Audit Committee or designated member would contact the PI and/or DF/HCC Sponsor-Investigator (when applicable), Director of OHRS and those responsible for oversight of the protocol within 24 hours of the audit finding notification. The Director of OHRS will notify the IRB and will take steps to close the study. A protocol, which has had accrual suspended because of any serious and/or continuing non-compliance issue(s), will be reported to the OHRP and the FDA, if appropriate.

If fraud or extreme carelessness is noted for a DF/HCC protocol, the Audit Committee Chairperson, or designated member, will notify the DF/HCC Associate Director for Clinical Trials, the DF/HCC Associate Director for Administration, the IRB and the applicable Division Chief. The Audit Committee Chairperson and the DF/HCC Associate Director for Administration may direct the OHRS to close the protocol immediately while an investigation takes place under the scientific misconduct procedures in place at DF/HCC and the home institution/s of the individuals involved.

All audits deemed "Unacceptable" or requiring immediate action undergo a complete audit report review, with an update on current protocol status, at the next scheduled Audit Committee meeting. In addition, the full audit report, PI's response and Audit Committee's determinations will be reported to the IRB Chairs for review.

Any protocol recommended for closure by the Audit Committee can only be reopened after the Audit Committee and the IRB determines the trial should be reopened.

If a PI has two or more "Unacceptable" audits within two years, the Audit Committee will send a written request to the PI's superior requesting a written plan for addressing the concerns raised by the multiple unacceptable audits.

APPEALS PROCESS

In cases where the PI feels that an audit was inaccurate or unfair and wishes to appeal, the PI may request an opportunity to address the Audit Committee at an open session. The PI must notify the Data & Safety Monitoring Manager of the request to attend the Audit Committee meeting after the final report is received. The PI should prepare and submit to the Clinical Research Auditor a formal written response to the audit findings prior to the scheduled meeting. The PI will have the opportunity to present and discuss their concerns with the committee members. During a closed session, the PI will be required to leave, and the Audit Committee will review the issues presented by the PI and make a determination.

In the event the PI feels the issues have not been addressed adequately, the appeal will progress to the DF/HCC Associate Director for Clinical Trials and the DF/HCC Associate Director for Administration. The PI must notify the Data & Safety Monitoring Manager of the request to appeal after the audit committee's decision is received and the appeal will be scheduled.

The PI will have the opportunity to present and discuss their concerns with the DF/HCC Associate Director for Clinical Trials and the DF/HCC Associate Director for Administration. The DF/HCC Associate Director for Clinical Trials and the DF/HCC Associate Director for Administration will review the issues presented by the PI as well as the Audit Committee's evaluation and make a final determination.

4.9 ADVERSE EVENT REPORTING

Policies and procedures for the DFCI IRB, or other IRB of record must be followed for the reporting of adverse events, IND/IDE safety reports, protocol deviations/violations/exceptions (other events), and unanticipated problems involving risks to subjects or others to the IRB.

The Principal Investigator must report all significant adverse events (AE) for drugs, biologics, procedures or devices to the IRB, to the protocol sponsor (including the NCI Program Director) and, when applicable, to national chairs of group studies, Institutional Bio-safety Committees, FDA and NIH/OBA (Office of Biotechnology Activities). All protocols are required to have a section describing the adverse event reporting requirements. For studies that require a report to be filed with other agencies (study sponsor, FDA, NIH/OBA, Institutional Biosafety Committees, etc.) submission to OHRS does not substitute for a report from the Principal Investigator to these agencies.

For trials where the DFCI IRB is the IRB of record, he PI must also report to the DFCI IRB external AE reports that meet the reporting criteria described in the DFCI IRB policy on Receipt and Review of IND/IDE Safety Reports. Trials not under the jurisdiction of the DFCI IRB must follow their IRB of record's reporting requirements for IND/IDE Safety Reports.

Other events generally involve the initiation of changes to the research without prospective IRB review and approval. These other events must also be reported to the sponsor and/or IRB of record per DF/HCC and IRB policy.

The IRB of record is responsible for reviewing and determining whether reported adverse or other events rise to the level of an unanticipated problem involving risks to subjects or others, or an issue of serious and/or continuing non-compliance. When the DFCI IRB is the IRB of record, OHRS is responsible for reporting these determinations to OHRP, FDA or other government agencies [21 CFR 56-108(b) (1) and 45 CFR 46].

DFCI IRB ADVERSE AND OTHER EVENT REPORTING REQUIREMENTS

The DFCI IRB policy requires the following AEs be reported for all subjects enrolled and actively participating in the trial, or when an AE occurs within 30 days of the last study intervention (e.g. drug administration):

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related / associated with the intervention.
- All Grade 4 (life threatening or disabling) Events – Unless expected and specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) Events

AE reports are submitted to the DFCI IRB per the DFCI IRB AE Reporting Policy. The DFCI IRB policy must be followed when reporting AEs experienced by any DF/HCC participants enrolled on a DF/HCC led study, including DF/HCC led Multi-Center trials where the event occurs at a non-DF/HCC site. The report should be made to the appropriate IRB of record.

IND/IDE SAFETY REPORTS

The DFCI IRB policy requires the investigator to report to the IRB within 60 days any IND/IDE safety reports that meet the following criteria:

- Serious or Life-Threatening; and
- Unexpected; and
- At least Possibly Related to the Research Intervention; and
- Has an implication for the conduct of the study under investigation using this study intervention (Example: the new risk changes the original risk benefit ratio of the study approved by the IRB. This would also apply to informing subjects previously treated with the agent of newly identified potentially serious long-term risks.)

It is the responsibility of the Principal Investigator to review IND/IDE safety reports as required by DF/HCC policy, and determine whether the report meets the criteria for reporting to the IRB.

Any sponsor correspondence requiring immediate action because of a serious adverse event/unanticipated problem and requiring modifications to a protocol, informed consent document or investigator's brochure (e.g. NCI Action letters) must be submitted as an amendment to the IRB per the IRB's policies. For studies under the DFCI IRB, this must occur within ten days of receipt.

OTHER RESEARCH RELATED EVENTS

Investigators are also responsible for conducting human subject's research in accordance with DF/HCC Policy, determinations, policies and procedures of the IRB of record, and all applicable Regulatory Sponsor requirements.

Non-compliance with these requirements during the conduct of a research study results in a protocol deviation, violation or exception and as such must be reported to the IRB of record.

- **Protocol Deviation:** Any expected departure from the defined procedures set forth in the IRB-approved protocol.
- **Protocol Violation:** Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.
- **Eligibility Exception:** Any request relating to eligibility criteria, e.g., enrollment of a subject who does not meet the inclusion/exclusion criteria.

The DFCI IRB further distinguishes between major and minor deviations and violations as follows:

- **Major Deviation/Violation:** a deviation or violation that impacts the risks and benefits of the study; may impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study.
- **Minor Deviation/Violation:** a deviation or violation that does not impact subject safety, compromise the integrity of study data and/or affect subject's willingness to participate in the study.

All major deviations must be reported to the DFCI IRB within five working days of when it is known that a deviation from the protocol is anticipated. Major violations must be reported within 10 working days of event discovery. All minor deviations/violations are documented according to institutional requirements, typically using a deviation/violation log. Minor deviation/violation logs are reviewed by the DFCI IRB at least annually at the time of continuing IRB review.

OTHER REPORTING GUIDELINES FOR DF/HCC CONDUCTED RESEARCH

Investigator-sponsored Research

The sponsor-investigator, as the holder of the IND/IDE, is responsible for reporting SAEs directly to the FDA via the FDA Form #3500a (Mandatory MedWatch Form).

In addition to the Mandatory MedWatch Form, the DF/HCC Sponsor-Investigator may also be required to complete a form supplied by the investigational drug supplier. DF/HCC investigators must comply with all reporting requirements, even if they differ from the IRB of record's reporting requirements.

Industry Sponsored:

In addition to IRB reporting requirements, the DF/HCC PI may also be required to report adverse events and other information to the study sponsor. The DFCI IRB reporting requirements may differ from sponsor requirements. DF/HCC investigators must comply with both.

Voluntary Reporting to FDA

The FDA's Form, #3500 (Voluntary MedWatch Form) may be used to voluntarily report serious adverse events, potential and actual medical product errors, and product quality problems associated with the use of FDA-regulated drugs, biologics, devices and dietary supplements.

Human Gene-Transfer Studies:

The PI must report all applicable adverse events to the NIH/OBA per the OBA Guidelines outlined in Appendix M-I-C-4: http://www4.od.nih.gov/oba/RAC/guidelines_02/Appendix_M.htm

5 CONFLICT OF INTEREST

5.1 OVERVIEW

A "Conflict of Interest" ("COI") may exist when an Investigator's individual interests, or those of his or her spouse or dependent child, have the potential to affect or be affected by his or her research activities. This can include financial interests, such as payment for services (such as consulting), stock or equity interests, and intellectual property rights. In addition, DFCI has incorporated research rules of the Harvard Medical School Policy on Conflicts of Interest and Commitment that address participation in clinical research activities where an Investigator has certain financial or business relationships to the research. Specifically, the DFCI COI policy's Clinical Research Rule and Research Support Rule prohibit participation in clinical research by an Investigator who:

- has received more than $25,000 in compensation annually from any entity whose technology is being investigated;
- has equity in any publicly traded entity whose technology is being investigated that exceeds $50,000 in value;
- has >1% equity in any publicly traded entity providing sponsored research support for the trial;
- has any equity interest in any privately held entity providing sponsored research support for the trial, or that owns the technology being investigated;

The policy's External Activity Rule and Executive Position Rule prohibit participation in clinical research by an Investigator who:

- serves in an executive role, or on a fiduciary board of directors, for any for-profit entity that provides sponsored research support for the research, or that owns the technology being investigated.

Investigators may not acquire any new impermissible interest until the later of (i) six months following the last day that a human study participant completes the clinical research (e.g., data lock plus 6 months), or (ii) the first publication of data derived from the clinical research, or a decision not to publish the data derived from the Clinical Research. Investigators may petition the COI Committee of their primary institution and HMS to rebut the Clinical Research Rule and/or the Research Support Rule. The presumptions may be overcome when, in the judgment of the primary institution's COI Committee and the HMS COI Committee, the Investigator holding the presumptively prohibited financial interests presents demonstrable, compelling justification – consistent with the rights and welfare of Clinical Research subjects – for being permitted to simultaneously hold the financial interest and participate in the clinical research. In addition to the petition process, certain limited policy exceptions may be granted upon review and approval by the investigator's primary institution and/or HMS (e.g., where an Investigator's impermissible financial interests result solely from his or her spouse's career activities).

5.2 DISCLOSURE OF OUTSIDE INTERESTS

DFCI faculty and research staff are required to comply with the DFCI Conflict of Interest and Commitment Policy (which incorporates the provisions of the Harvard Medical School Policy on Conflicts of Interest and Commitment), and with applicable COI policies of other institutions with which they are professionally affiliated. They must disclose their financial interests, as well as those of their immediate family members that are related to their institutional responsibilities, and therefore could have real or apparent conflict with their research, regardless of the source of research funding. Investigators from other DF/HCC sites are similarly bound by the COI policies of

their institutions and must disclose their financial interests as required by their primary institution. However, as described below, all clinical investigators participating in research reviewed by the DFCI IRB must complete an investigator disclosure form, which is submitted to the OHRS with the protocol if a financial interest is reported.

5.3 IDENTIFYING AND MANAGING INVESTIGATOR CONFLICTS OF INTEREST

DFCI has entered into a Reciprocal Institutional Review Board Reliance Authorization Agreement with DF/HCC institutions ("Relying Institutions"), whereby it serves as the IRB of record for all cancer-related clinical trials requiring scientific review ("Reviewing Institution"). To streamline processes, these same institutions have agreed to rely on DFCI's COI office for initial review of financial interest disclosures for protocols submitted to the DFCI IRB. Every Investigator participating in these clinical trials must provide a protocol-specific financial interest disclosure with the protocol submission to DFCI, even if the research will not occur at DFCI. DFCI is then responsible for the initial review and identification of potential COI policy violations for all Investigators. If a potential violation of the DFCI and HMS COI Policy is identified, DFCI refers the matter to the investigator's primary institution to determine the appropriate strategies to manage, reduce, or eliminate the conflict, if possible. These measures may include, for example, elimination of the financial interest, disclosure of the financial interest in the informed consent form, the utilization of enhanced data safety oversight mechanisms, or independent data review and monitoring.

5.4 IDENTIFYING IRB/ SRC CONFLICTS OF INTEREST

The committee members are notified of the conflict of interest policy on every agenda, and members recuse themselves if there is a conflict of interest with the protocol being reviewed. If a conflict of interest exists between a reviewer and his/her assignment, it is the reviewer's responsibility to notify the OHRS meeting coordinators upon receipt of the meeting packet.

At every IRB and SRC meeting all reviewers must indicate any COI on a disclosure form, which states the following:

Financial Interests of Committee Members: Committee members are required to recuse themselves from the discussion and vote on protocols where they have a financial interest with the sponsor, except to provide information at the committee's request prior to the deliberation and vote on the protocol. *Committee members* review the list of projects *being considered* and *indicate* if *they,* or *an immediate* family member, have any financial interest, which can include, but is not limited to the following:

- **Participation in the project**: If a member is listed on the protocol/project or will be included (or reasonably may be expected under academic standards to be included) as a co-author on a publication of the project's results.
- **Financial interests**: If a member or an immediate family member has or is:
    - An interest in a business that is supporting or facilitating the project, or a business that is known to the committee member to own (or have license rights to) the technology that the project is on:
    - Receiving ANY FINANCIAL COMPENSATION (not including reimbursement of reasonable travel and other expenses) from a business for any reason, including but not limited to consulting, royalties (whether received directly or through the hospital), attending or speaking at conferences, or being employed; or

- Having any equity interest in a business, except for an interest of less than $30,000 in a publicly held, widely traded business.
- An ownership interest in a patent or a patent application covering the technology that the committee member knows the project is on.

- **Other financial interests**: Such as serving as a board member (of a board of directors or scientific advisory board) or as a consultant or executive to a business that is supporting or facilitating the project, or that owns or has license rights to the technology the project is on.
- **Other interests:** Anything else that may raise a real or perceived conflict.

All conflicts will be noted and recorded in the minutes of each meeting along with an attestation confirming disclosure based on the above statements.

6 EDUCATION

The Office of Data Quality (ODQ) provides educational opportunities to clinical trial researchers through a range of programs and services. ODQ provides access to focused education on clinical trials to DF/HCC investigators and their research teams; serves as a liaison between investigators and the NCI to ensure effective communication and to meet NIH/NCI clinical trial management requirements; and designs study management tools and templates needed to meet regulatory and institutional requirements.

The ODQ Clinical Trials Education Coordinator facilitates the following educational opportunities:

Human Subject Protection (HSP) and Good Clinical Practice (GCP) Training: DF/HCC has selected the Collaborative Institutional Training Initiative (CITI) education program as the preferred method of HSP and GCP training for all personnel participating in research under its auspices. Researchers must complete HSP and GCP courses appropriate prior to participating in research. Re-certification for both HSP and GCP training is required every three years

New Principal Investigator (PI) Training: A mandatory training on responsibilities and expectations incurred as an investigator under the DF/HCC.

DF/HCC Clinical Research Support Website: An online resource that investigators and research staff may use to access current policies, operations and guidance, as well as e-learning modules and other educational resources for conducting research at DF/HCC.

Research Staff Education Series: This series provides a forum for education and discussion regarding the issues that investigators and research staff confront. Topics cover ethical issues in clinical research, barriers to day-to-day trial management, and clarifications about how to apply regulations and guidelines to current practice.

CTSC Investigator Training Program: In addition to oncology-specific training experiences, faculty and trainees have access to the training programs, seminars and related activities sponsored by Catalyst (www.catalyst.harvard.edu), Harvard's NIH-funded clinical and translational science center (CTSC). Catalyst has an

array of clinical investigation training programs and resources. Its website has a catalog, with video links, of training programs.

In addition, the Office of Data Quality appoints a representative to chair the Education Working Group. This group, which includes representatives from OHRS, RIO, and the institutional Clinical Trials Offices, meets regularly to discuss upcoming educational needs and to evaluate and strengthen DF/HCC communications for research staff. The ODQ chair of this working group represents the group at CLINOPS.

7 DEFINITIONS

Clinical Trial: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. (NIH Policy, 2015)

Adverse Event (AE or Adverse Experience): Any untoward medical occurrence associated with the use of drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable or definite). (NCI Guidelines: Adverse Event Reporting Requirements, September 2013)

Serious Adverse Event: Any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1. Death.
2. A life-threatening adverse drug experience.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. A persistent or significant incapacity or the substantial disruption of the ability to conduct normal life functions.
5. A congenital anomaly/birth defect.
6. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (21CFR312.32a) (NCI Guidelines: Adverse Event Reporting Requirements, September 2013)

Life-threatening Adverse Event: Any adverse event that places the subject, in the view of either the investigator or the sponsor, at immediate risk of death from the AE as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death (21CFR312.32a, ICH E2A) (NCI Guidelines: Adverse Event Reporting Requirements, September 2013

Expectedness (Unexpected Adverse Event): An unexpected AE is any AE, the specificity or severity of which is not consistent with the current Investigator Brochure IB); or the Instructions for Use or other device documentation; or, if an IB or equivalent is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the IND/IDE (21CFR312.32 and/or

21CFR812). Additionally, the ICH E2A defines an unexpected adverse drug reaction as an AE, the nature and severity of which is not consistent with the applicable product information (e.g., IB for investigational agent). (NCI Guidelines: Adverse Event Reporting Requirements, September 2013)

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily "caused by a therapeutic intervention". After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Definite: The adverse event is clearly related to the intervention.
Probable: The adverse event is likely related to the intervention.
Possible: The adverse event may be related to the intervention.
Unlikely: The adverse event is doubtfully related to the intervention.
Unrelated: The adverse event is clearly NOT related to the intervention.
(NCI Guidelines: Adverse Event Reporting Requirements, September 2013)