

DANA-FARBER/HARVARD CANCER CENTER

Institutional Data and Safety Monitoring Plan

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1. Introduction

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

For the purposes of this document, the operational definition of a clinical trial as defined by the National Cancer Institute (NCI) is: "a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer but at risk for it." Further clarification of this definition can be found at:

http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page2#op_def .

2. Monitoring the Progress of Trials and the Safety of Participants

2.1. Overview

While 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. DF/HCC trials are monitored in many ways during development, review and performance throughout the lifecycle of the research protocol. All oncology trials in DF/HCC go through a central protocol review and monitoring system (PRMS) as well as a data and safety monitoring process. This includes several consortium wide committees that provide institutional oversight including the Scientific Review Committee (SRC), DFCI Institutional Review Board, Scientific Progress Review Committee (SPRC), Clinical Investigations Leadership Committee (CLC), Audit Committee, Data Safety Monitoring Committee, Data and Safety Monitoring Board and Multi-Center Coordinating Committee. Additional monitoring processes, such as central participant registration and central management of research data, are incorporated into the DF/HCC institutional data safety monitoring process. Individuals from DFCI, MGH, BWH, CHB and BIDMC serve as members on all clinical trials committees. Similarly, all Disease Programs have representation from participating DF/HCC institutions. All protocols with cancer as the primary disease fall under the jurisdiction of the DF/HCC SRC and DFCI IRB, which by agreement serves as the IRB of record for cancer-related therapeutic and non-therapeutic trials conducted through DF/HCC.

Please refer to Appendix I & II, which describe the overall structure of the clinical trial support function and Appendix III, which describes the clinical trials process.

2.2. Institutional Oversight of Clinical Trials

2.2.1. Prior to Protocol Activation

2.2.1.1. Disease Program Review

Disease Programs include representation from all participating institutions. They review and approve all proposed protocols for feasibility and determine priority within the Disease Program. Protocol documents include a protocol specific monitoring plan and should include reference to the DF/HCC Data and Safety Monitoring Plan (DSMP).

2.2.1.2. SRC/PSRC

As part of the PRMS, the Scientific Review Committees (SRC) review for scientific merit and feasibility the protocols referred by the Disease Programs. For clinical trials there are two Adult and one Pediatric SRC involved in this comprehensive review process. A fourth SRC reviews non-clinical research trials. Each committee is made up of members with expertise necessary to make the scientific decisions.

The Scientific Review Committee (SRC) reviews all cancer trials involving adult subjects. The Pediatric Scientific Review Committee (PSRC) reviews similar protocols involving pediatric subjects. For protocols involving adult and pediatric subjects, review will be conducted by the committee that represents the population that will have the most subjects accrued on the trial and the other committee will have one member participate in that review as a representative for the other population. The scientific review committees review the novelty and importance of the therapeutic 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 underway.

The scientific review committees are comprised of physicians and biostatisticians. Representatives from radiation safety, biosafety, pharmacy and nursing departments also attend the meetings.

The committees are notified of the conflict of interest policy, as outlined in section 2.4, 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 assigned project, it is the reviewer's responsibility to notify the OHRS upon receipt of the meeting packet. Ad hoc reviewers may be assigned if deemed necessary by the SRC Chairperson.

The Pediatric Scientific Review Committee (PSRC) reviews all risk studies involving pediatric patients, and ensures that the protocol is of appropriate scientific and therapeutic merit and is in accordance with the scientific plan of the Institute. All investigators from the Division of Hematology/Oncology at Children's Hospital or the Department of Pediatric Oncology at the Dana-Farber Cancer Institute must submit protocol to the PSRC for review and approval. The committee chairperson appoints the membership. Committee membership includes physicians and

biostatisticians. Representatives from pediatric nursing, pediatric pharmacy and Children's Oncology Group (COG) clinical research coordinators also attend the meeting. The committee may supplement its membership at any time to ensure proper scientific review. The PSRC Chair may call upon the support of ad hoc reviewers for assistance in areas of expertise, balance of review, unavailability of other appropriate reviewers, etc.

The Office of Human Research Studies (OHRS) administrates and supports the P/SRCs for DF/HCC and provides all documentation for actions by the P/SRCs. All required documentation is centrally maintained in this office. (The Senior Director of OHRS, reports directly to the DFCI Senior Vice President for Research and Institutional Official/DF/HCC Associate Director for Administration.)

Scientific review occurs prior to IRB review. New protocols are not forwarded to the IRB until a determination has been made that the investigators have adequately responded to all conditions for P/SRC approval. Amendments may also require review by the P/SRC, before DFCI IRB review.

2.2.1.3. IRB

Seven IRB panels, which are registered with the US DHHS, Office of Human Research Protection (OHRP) Panel A, B, C, D, E, F and G, review and approve all new and continuing protocols focusing on risk vs. benefit for the participants involved in research, and assure their protection to the maximum extent possible. The above review processes include multi-modality physicians, nurses, pharmacists, unaffiliated community members, biostatisticians, and administrative staff who review using their various areas of expertise for the committees. The panels meet the regulatory requirements for meeting operations.

The Office of Human Research Studies (OHRS) administrates and supports the IRBs for DF/HCC and provides all documentation for actions by the IRBs. All required regulatory documentation is centrally maintained in this office. (The Senior Director of OHRS, reports directly to the DFCI Senior Vice President for Research and Institutional Official/DF/HCC Associate Director for Administration).

The most recent version of the protocol, consent document, eligibility checklist, and disease program priority lists are maintained by the OHRS on the computerized Oncology Protocol System (OncPro) which is available to all Investigators and research staff at DFCI, BWH, MGH, CHB, BIDMC, and authorized network affiliates. The Overall PI or designated research team member is responsible for keeping sites that do not currently have access to the online system updated on changes.

On behalf of DF/HCC, DFCI IRBs are formally designated to review and monitor research involving human subjects to protect the rights and welfare of the subjects. They also provide oversight and monitoring of such protections. The mission of the IRBs is to review research involving human subjects and to ensure that the risks and

benefits of the research are appropriate and to ensure that there is full compliance with Federal regulations for the protection of human subjects in research.

Federal regulations at 45 CFR Part 46 require that institutions engaging in human subject research supported by the Department of Health and Human Services (DHHS) devise mechanisms for the protection of human subjects. The regulations require that each institution conducting human subject research file a written “Assurance” of protection for human subjects and designate one or more Institutional Review Boards (IRBs) to review its human subject research. The IRBs must comply with the requirements of all relevant regulatory agencies including the DHHS Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA).

The IRBs review all 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. 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. The IRBs have the authority to observe and/or monitor DF/HCC research to whatever extent it considers necessary to protect human subjects. No official or committee of a DF/HCC institution may permit the conduct of human subject research that has not been approved by the IRB.

The independence of the IRBs and the protection of human subjects in research are the paramount priorities of the DF/HCC. To that end, the OHRS Senior Director, OHRS Deputy Director and IRB Chairs may at any time meet with the DF/HCC Center Director or DFCI Legal Counsel or other appropriate senior officials for any reason relative to the protection of human subjects in research.

The IRB Chairs will appoint IRB members to serve for three-year terms, however, there are no term limits placed on length of service. Candidates for membership on the IRB may be recommended to the IRB Chairperson by the OHRS Senior Director, and/or officials of the DF/HCC institutions that conduct human subject research reviewed by the DFCI. 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 as follows:

- Each IRB will have at least five members;
- IRB members will possess varying backgrounds to promote complete and adequate review of research activities commonly conducted at this Institution and institutions for which the DFCI IRB is the designated IRB;

- IRB members will be sufficiently diverse relative to race, gender, cultural background, and sensitivity to community attitudes so as to promote respect for the IRB's advice and counsel in safeguarding the rights and welfare of human subjects;
- IRB members will include persons able to ascertain the acceptability of proposed research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice;
- IRBs will consist of qualified persons of both sexes;
- No IRB will consist entirely of members of one profession;
- Each IRB will include at least one member whose primary expertise is in a scientific area;
- Each IRB will have at least one member whose primary concerns are in non-scientific areas; and
- Each IRB will include at least one member who is not otherwise affiliated with this Institution and who is not part of the immediate family of a person who is affiliated with this Institution or other institutions for which the DFCI IRB is the designated IRB.

Members vote to approve, require modifications in (conditionally approve), disapprove, or defer research submitted to the IRB. Members are expected to attend IRB meetings on a regular basis, serve as primary reviewers for research within their areas of expertise, and serve as general reviewers on all research discussed at convened meetings. Members may be asked to conduct expedited reviews on behalf of the IRB.

Scientific members will have had experience in research involving human subjects, and will be recruited from staff among a DF/HCC institution or from the community.

Non-scientific members may have expertise in human rights or social issues and/or ethical or legal issues considered to be relevant to human subject research, and will be recruited from staff among a DF/HCC institution or from the community.

Unaffiliated community-based members, and members of their immediate families, will have no formal or informal affiliation with DF/HCC institution, other than their service on the IRB.

At its discretion, each IRB may recruit (non-voting) consultants (sometimes referred to as "non voting or ex officio" members) whose presence at the meetings would aid the IRB in conducting its duties. Attendance by an Ad Hoc Consultant who is not otherwise a member of the IRB will be requested by the IRB Chair, OHRS, or the Primary Reviewer of the protocol, as appropriate. The IRB may include an Attorney appointed by the Institution's General Counsel to serve as a Continuing Consultant

(i.e., non-voting member) to the IRB. In this capacity, the attorney will advise the IRB as to fulfilling its function to protect the rights and welfare of human subjects.

2.2.2. Post Activation and Ongoing Monitoring

2.2.2.1. IRB

Continuing Review occurs at least annually for all protocols under the jurisdiction of the DFCI IRB with the exception of qualifying non-federally funded minimal risk studies. For clinical trials the review focuses on the risks, benefits, adverse event reports, other events (including deviations, violations, exceptions and unexpected problems) and the overall progress of the research.

Amendments are reviewed by the DF/HCC SRC, if applicable and the DFCI IRB and processed by the OHRS with the appropriate notification and documentation.

The IRB determines when it is necessary to inform participants of any new findings that reveal additional risk or information that may alter their willingness to participate in the trial.

Panels C,F, and G of the IRB primarily review Continuing Reviews, Amendments, Other Events including Deviations, Violations and Exceptions, SAE reports and Unanticipated Problem reports pertaining to clinical research. (Although the other IRB panels have the expertise to review the same events.) These committees closely scrutinize these reports and summary listing of SAE reports per protocol. When there is any question, the PI is questioned further and more information is obtained. When action is needed, the committee may propose and carry out any action deemed necessary. These actions relate to all participating institutions.

2.2.2.2. Scientific Progress Review Committee (SPRC)

Per NCI guidelines, DF/HCC conducts an annual scientific progress review of its clinical trials. The SPRC is responsible for performing the annual scientific review of protocols, including a review of study accrual, outcomes, and the feasibility for completion of the study within a reasonable time frame. This includes review of any new scientific findings or changes to the protocol that may affect the likelihood of completion of the study. The SPRC also is responsible for monitoring trial accrual and has the authority to close trials due to slow accrual. Beyond this, the SPRC monitors the progress of publications for those trials that have completed enrollment. The SPRC inter-institutional membership is appointed through the President of DFCI, who also serves as the Director of DF/HCC, or his designee. The committee is comprised of the Scientific Progress Chair, faculty actively engaged in the conduct of clinical trials and representatives from Biostatistics, Office of Human Research Studies and Quality Assurance Office for Clinical Trials. The SPRC, part of our PRMS, meets monthly and reviews trials by disease program.

Protocols are reviewed at least once a year for slow or inadequate accrual, based on DF/HCC's slow accruing policy, which defines specific parameters for trial accrual. Accrual reports by disease program are submitted to the Scientific Progress Review Committee (SPRC). The SPRC recommends the appropriate action which may include more frequent monitoring or closure of a trial. Zero accruing protocols are reviewed twice a year and reports provided to the SPRC semi-annually. Fast accruing protocols are monitored monthly and reports provided to the SPRC semi-annually to be sure they are proceeding in a safe and effective way.

2.2.2.3. Clinical Investigations and Leadership Committee (CLC)

2.2.2.3.1. Overview

Clinical Investigations Leadership Committee (CLC) provides a regular forum for the senior clinical investigations 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. DF/HCC has found CLC to be essential in its effort to function as a single entity for clinical trials despite the reality of its consortium structure.

The CLC reviews clinical investigations activities, processes, and systems, as well as DF/HCC issues that require senior-level, inter-institutional attention. While separate and distinct from the PRMS and DSMP processes, the CLC galvanizes the efforts of the DSMP, which focuses on the auditing, monitoring, and performance of active clinical trials, as well as the PRMS, which focuses on the scientific merit, feasibility and priority of trials. By being able to look globally at issues that have an impact on the effectiveness and efficiency of DF/HCC's clinical investigations process, the CLC 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 CLC 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, senior representatives from DF/HCC member institutions, and/or IRB, as appropriate. New and revised policies and procedures developed by CLINOPS may be distributed to CLC members for additional comment and review; issues related to implementing such policies and procedures at DF/HCC institutions may be referred to CLC. 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 CLC.

The CLC 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

Annually, the CLC Chair 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 as a result of CLC efforts. Throughout the year, issues requiring the prompt attention of the Center Director or Executive Committee are communicated, as needed.

Depending on the circumstances, CLC 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 Coordinating Committee, Administration, and Medical Director of Clinical Trials Operations. CLC may identify issues that require implementation or follow-up by one of the DF/HCC institutions. The CLC Chair, with the advice of the Medical Director of Clinical Trials Operations, Associate Director for Administration and, as needed, the Center Director, determines the best possible process for conveying and resolving these concerns.

2.2.2.3.2. Membership

The Center Director, or his designee, appoints all CLC members, including the CLC 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-R for DFCI; Medical Director, Clinical Trials Operations, DF/HCC; IRB Chair(s); Director, DF/HCC Research Pharmacy; Senior Director, Office for Human Research Studies; biostatistics representative; and faculty leaders in clinical trials (preferably faculty who are also on the Executive Committee) and administrative representatives from the DF/HCC member institutions.

2.2.2.3.3. Meeting Structure

Generally, the CLC will meet once a month during the academic year, or not less than nine times a year. CLC members will vote on any formal change in meeting date. The auditing and monitoring segment of the meeting usually occurs first, followed by the clinical investigations issues segment. 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 CLC Chair and Vice Chair as well as the Medical Director for Clinical Trials Operations and Associate Director for Administration serve as an ad hoc executive committee if there is an immediate issue that needs to be addressed before the next scheduled or emergency meeting can be convened.

2.2.2.3.4. Inter-Institutional Representation

Because of its inter-institutional composition, CLC 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 CLC can communicate clinical trials-related concerns. This individual serves as a member of CLC 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 CLC regarding actions taken at each institution in response to CLC-identified matters. Each institution is also responsible for identifying the appropriate administrator at the institution to whom CLC can communicate clinical trials-related concerns.

Through participation in CLC, institutional representatives are kept apprised of clinical trials issues and have an opportunity to ask questions or raise issues. Following a CLC meeting, issues requiring follow-up are referred to the appropriate body or individual, including, but not limited to, the Center Director, Executive Committee, Clinical Sciences Coordinating Committee, and/or member institution leadership.

The Chair is responsible for determining the best process for communication and follow-up regarding matters identified by CLC. This is done in consultation with the DF/HCC Associate Director for Administration and Medical Director for Clinical Trials Operations. CLC institutional representatives are responsible for following up on issues relevant to their institution that are discussed at CLC meetings or brought to their attention. They are responsible for keeping CLC and/or DF/HCC leadership, as appropriate, apprised of the status and resolution of such matters.

2.2.2.3.5. Staff Support

QACT coordinates meetings and is responsible for maintaining the records for this committee. The minutes from meetings are considered peer-reviewed.

2.2.2.3.6. Data and Safety Monitoring Process

Consistent with NCI Guidelines, the DF/HCC data and safety monitoring process is responsible for the data and safety monitoring of trials at DF/HCC.

This encompasses three committees: the Audit Committee, Data and Safety Monitoring Committee (DSMC), and Data and Safety Monitoring Board (DSMB). These Committees have the relevant authority to promote high standards of clinical trial conduct. Given its multi-institutional organizational structure, DF/HCC created an additional committee, the CLC, which, while not required by NCI Guidelines, is necessary in order to provide appropriate identification and coordination of issues related to the conduct of clinical trials. By creating the CLC, DF/HCC ensures an inter-institutional forum for identification and resolution of issues. It also offers the critical opportunity to synthesize information and identify global issues related to the DSMP that require senior level decision-making.

The CLC serves as an umbrella entity, providing a needed forum for senior leaders to review the reports, activities and trends, including those related to the DSMP. The CLC's goal is to synthesize this information in order 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.

2.2.2.4. Clinical Trials Operations Committee (CLINOPS)

The Clinical Trials Operations Committee (CLINOPS) is a component of DF/HCC's Clinical Research Unit, which is an NCI-approved Shared Resource. 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-wide clinical trials operating policies and procedures. Members include key representatives with clinical trials responsibilities from DF/HCC member institutions, including but not limited to such areas as nursing, pharmacy, information services, and data management. Minutes of the CLINOPS meetings are maintained by the QACT.

2.2.2.5. Audit Committee

The Audit Committee facilitates the review of the DF/HCC internal audit program, to provide clinical input for the audited protocols and identify any needed DF/HCC system changes that may be brought to light through the internal audits.

The Audit Committee meets monthly to insure timely oversight of internal and external audits.

The Audit Committee reviews all internal audit reports provided by the clinical research auditors. The committee discusses the protocol audit findings and their ratings based on the DF/HCC standardized audit performance evaluation scale. The committee decides when corrective action and/or education are needed to ensure quality improvement.

The Audit Committee reviews reports of external audits provided by the Quality Assurance Office for Clinical Trials (QACT) to ensure that DF/HCC is aware of audit activity and findings. The Audit Committee will determine if an internal audit or follow-up action is necessary.

The Audit Committee provides a monthly summary report to the Clinical Investigations Leadership Committee (CLC) of the audits reviewed, the ratings given, and any issues that were identified at the last meeting. The Audit Committee can also refer any major problems that have been identified to CLC.

The Audit Committee oversees the auditing process including the results, methods, reporting and ultimately the educational opportunities. Additionally, the committee has oversight of the auditing program's impact on the DF/HCC policy and procedures and regulatory compliance. The Quality Assurance Office for Clinical Trials (QACT) manages the administrative tasks of the Audit Committee. The audit reports are confidential.

Members and the chair of the Audit Committee are appointed for a minimum of three years by DF/HCC Associate Director for Administration, who is also the Senior Vice President for Research (SVP-R) for DF/HCC. Membership includes representation from the DF/HCC institutions, as well as, biostatistics, pharmacy, nursing, the Director of Office of Human Research Studies (OHRS) and the Director of the QACT.

A quorum consists of a minimum of 6 of the voting members, including at least one physician.

2.2.2.6. Data and Safety Monitoring Committee (DSMC)

The DF/HCC Data and Safety Monitoring Committee (DSMC) reviews high-risk pilot, Phase I and Phase II protocols for data and safety issues. High risk relates to pediatric trials, first time in human trials, gene transfer trials, multi-center trials and any other trial as deemed necessary. The review consists of information provided by the study teams as well as data provided by the Quality Assurance Office for Clinical Trials (QACT). The DSMC communicates information to the IRB as necessary. The Center Director appoints the Committee chair. The chair selects members, with the concurrence of the Associate Director for Administration.

The committee was initiated in October of 2002 and is responsible for reviewing Pilot, Phase I or II high risk protocols and protocols requiring very close monitoring such as gene transfer protocols. High risk protocols include:

- Pilot, Phase I or I/II trials which involve the use of a drug for the first time in adults and/or children
- DF/HCC PI-initiated or led, Pilot, Phase I or I/II trials, including DF/HCC initiated multi-center trials
- Vaccine trials using live or attenuated viruses
- Gene transfer protocols

- Unusually complex or intensive protocols
- Studies involving an IND held by a DF/HCC PI

This committee consists of internal DF/HCC faculty and staff to allow the meetings to occur quarterly and/or more regularly if required. The QACT provides administrative support for the DSMC. The PI must complete a monitoring form that describes toxicities and study progress for each protocol that has been identified as high risk. In addition to the completed protocol's monitoring form, serious adverse event reports, adverse events listings and missing form reports are provided to each reviewer. Reviewers are assigned to each protocol and they present the review at the meeting. Follow-up occurs as needed and the protocol is continuously monitored until completion. Meeting summary reports are provided to the IRB and CLC after each meeting.

2.2.2.7. Data and Safety Monitoring Board (DSMB)

A centralized Data and Safety Monitoring Board (DSMB) has been created to review DF/HCC investigator-initiated large randomized protocols that otherwise do not have an independent DSMB assigned. These trials include both NCI- and industry-sponsored large randomized studies, typically Phase III trials, which have a DF/HCC investigator as the lead investigator. The Quality Assurance Office for Clinical Trials (QACT) coordinates the meetings.

Guidelines set for the DSMB reviewers include: (1) Familiarizing themselves with the research protocol(s) and plans for the data and safety monitoring. (2) 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. (3) Reviewing reports of related studies to determine whether new information means the monitored study needs to be changed or terminated. (4) Review in 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). (5) Following each DSMB meeting, provide the study team with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing or terminating the trial. The DSMB provides a summary of the board findings to the IRB, CLC and the principal investigator.

The DSMB membership includes the voting membership of the board who is appointed by the Senior Vice President for Research. The DSMB chair is selected from the voting members. 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 DSMB.

Chair, Medical Oncologist (External, outside DF/HCC)
Medical Oncologist (External, outside DF/HCC)
Medical Oncologist (DF/HCC)

Other Scientist (radiologist or surgeon –within DF/HCC)
Statistician (External, outside DF/HCC)
Ad Hoc membership (if special expertise is needed)

A representative from the Department of Biostatistics and Computational Biology will serve ex officio as a non-voting member of the DSMB.

With the prospective permission of the DSMB Chair, guests may attend a DSMB meeting to observe for educational purposes. The invited guest will be required to sign a confidentiality agreement prior to the meeting. If the invited guest is affiliated with any of the trials under review, he/she will be asked to leave for the closed session review of that trial.

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.

The meeting is held at least semi-annually depending on the nature and volume of the trials being monitored. Each meeting will have 3 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 should 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 to summarize and evaluate the overall meeting, and to plan the next meeting. The meeting may occur by conference call if necessary.

Both the DSMB minutes and PI reports will usually not include confidential outcome data. For studies that remain blinded, outcome data will not be made available to individuals outside of the DSMB. 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 protocol PI a rationale for these recommendations.

Outcome data for protocols still enrolling patients are considered confidential and are not to be discussed outside the DSMB meetings. Outcome data may be released to the study team for manuscript preparation or planning of future studies only after review and approval by the DSMB. No communications of the deliberations (either written or oral) or recommendations of the DSMB will be made outside the DSMB except as provided for in this policy.

The study team should implement recommendations from the DSMB expeditiously. When requested by the DSMB, the protocol PI will respond in writing to the DSMB

and DFCI IRB of the actions taken regarding the recommendations and the reasons for that decision. The DFCI IRB will adjudicate any disagreements between the DSMB and the protocol PI.

Trials being monitored by the DF/HCC DSMB will remain under the DF/HCC DSMB review until either the last enrollment occurs, or until the DSMB feels there are no patient safety concerns that require further monitoring. The DSMB will determine the length of continued review on a study-by-study basis.

The DF/HCC expects that the DSMB will act in a way that is 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 either the assumptions made in the original design are not true, or because of data external to the study. The deliberations of the DSMB should not be influenced by special interests of either the study team or the protocol sponsor.

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

2.2.2.8. Multi-Center Coordinating Committee (MCC)

The Multi-Center Coordinating Committee (MCC) was created in November 2007 to provide assistance in the development of a PI-initiated multicenter trial, assure a prospective plan for auditing and monitoring has been established and ensures adequate resources are in place to conduct the multi-center trial in compliance with regulations and policies.

The MCC is composed of representatives from the Quality Assurance Office for Clinical Trials, the Clinical Trials Education Office, the Clinical Trials Agreements Office and the PI's site Clinical Trials Office. Each MCC member has expertise representing different aspects of the multicenter trial review process including registration process, data management, auditing, investigator qualifications, regulatory reporting requirements, monitoring and resources.

Prior to any external participating site becoming involved with the trial, defined as sites outside of DF/HCC and the DF/PCC Network Affiliates, MCC approval is required. As part of the MCC review process the investigator, as Sponsor, is required to submit the following to the MCC:

- Protocol
- Site Qualification Questionnaire for each participating site to determine if participating sites meet DF/HCC and protocol requirements
- Protocol specific multi-center data and safety monitoring plan (DSMP) for interventional trials, using DF/HCC templates, which establish a plan for central registration, collection of SAEs, deviations, and violations and

mechanisms to report this information to DF/HCC and to all participating locations. *For non-interventional trials, appropriate monitoring language must be incorporated into protocol document.*

- MCC Checklist and MCC International Checklist, as applicable, which outline resources, responsibilities and coordinating centers prospective plan for fulfilling requirements.

The MCC then meets with the PI and study team to review the protocol, multi-center DSMP, Site Qualification Questionnaires and MCC Checklist to ensure all criteria for conducting a PI-Initiated multi-center trial are met. The meeting requirement may be waived for non-interventional trials if the MCC determines an exemption from the MCC is appropriate.

Once all criteria have been met, the MCC will sign-off on the multi-center DSMP by sending a MCC Completion Form to the PI and study team. PI and study team are expected to submit the MCC Completion Form to the IRB as verification that preliminary requirements have been put in place to ensure the safe and consistent conduct of research. The MCC may issue an approval, conditional approval or exemption.

2.2.2.9. Registration

All participants are enrolled in clinical trials through the Quality Assurance Office for Clinical Trials (QACT). Eligibility checklists are reviewed and approved by the QACT Protocol Registrar prior to registration. Signed consent forms are verified for appropriate signatures and only the correct document downloaded from OncPro with the appropriate IRB approval date is accepted.

In addition, Phase I dose escalations are continuously monitored by the QACT to be sure that the appropriate number of participants are entered at each dose level per protocol design.

2.2.2.10. Data Management (QACT)

The data from DF/HCC-initiated trials or NCI-sponsored therapeutic trials that do not have data management by the sponsor are computerized in the Quality Assurance Office for Clinical Trials (QACT). This involves a formal process of case report forms design, forms testing, computerization of data, data querying for missing or ambiguous data, and data cleaning. Reports are generated for the study team as requested and the data are analyzed by the Cancer Center biostatisticians.

The QACT Data Analysts manage the computerized databases for DF/HCC initiated in-house clinical trials. The Data Analysts:

- Design data collection forms for clinical trials
- Initiate, maintain and quality control the computerized data for the projects
- Maintain documentation for database, and integrity of the database
- Provide quality control on data collection methods
- Monitor the submission of data of the clinical trials

- Prepare data for analysis
- Produce regular reports requesting missing data and updates provide program reports for the study teams
- Assist in training of research staff in data collection methods.

The QACT Data Analysts interact with the study team including, the Principal Investigators, Research Nurses, Study Coordinators, and Biostatisticians for quality data assurance and management.

Problems with obtaining data or data quality are referred to the trial monitor, auditing program or to CLC, depending on the severity of the circumstances. Problems with suspected misconduct are reported to the Vice President for Research.

2.2.2.11. Education

The DF/HCC Clinical Trials Education Office's (CTEO) mission is to advance clinical research by empowering investigators and study staff to conduct high quality clinical research. This office sets the standards for education and provides a structure for ensuring training of DF/HCC investigators and study staff prior to participating in the clinical research process. Through a range of programs and services, CTEO develops and 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. This office also maintains the online *Guide to Human Research Activities* and supports the NCI Investigator Registration process.

The CTEO facilitates the following educational opportunities:

1. Investigator Good Clinical Practice (GCP) Training Course: Harvard faculty and other experts in the DF/HCC research community developed this online course to address key concepts in good clinical practice as they apply to oncology research. The modules, ten for clinical researchers and eight for non-clinical researchers, are viewed on screen, followed by a brief online quiz. This is a mandatory one-time requirement for new researchers or experienced investigators new to DF/HCC. This is a Category 1 CME approved course.

2. New Overall Principal Investigator (PI) Briefing: A mandatory one-to-one review of responsibilities and expectations incurred as an investigator.

3. DF/HCC Clinical Investigator Education Series: This category 1 CME approved program is offered quarterly and addresses topics of interest identified by DF/HCC leadership and/or clinical investigators.

4. eLearning Center: An online resource library that references key presentations, policies, and general information to help investigators and research staff meet their day-to-day research responsibilities.

5. Research Staff Orientation: This online program addresses topics pertinent to conducting research at DF/HCC.

6. Research Staff Education Series: This monthly series provides a forum for 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.

7. Human Subject Protection Training: DF/HCC has selected the Collaborative Institutional Training Initiative (CITI) education program as the preferred method of training for all personnel participating in research under its auspices. The CITI training consists of two “Core” courses {Biomedical and Social/Behavioral Research (SBR)}. The modules, developed by experts in the “IRB Community”, include material that can be read on screen or printed, followed by a brief on-line quiz. Re-certification is required every three years.

8. IND Support and Oversight: The DF/HCC CTEO provides standardized tools and internal guidance sheets to support IND development and management across the institutions. Each individual institution’s clinical trials office is responsible for providing infrastructure to support the day to day management of these trials.

2.2.2.12. Pharmacy

The DF/HCC research pharmacy representatives from DFCI, BWH, MGH, CHB, and BIDMC meet regularly with representatives from the Clinical Trials Operations Committee to review the policies and procedures in place that relate to investigational drugs. Topics include drug procurement and storage, drug accountability logs, dispensing, training, quality control procedures and other investigational drug issues. The research pharmacists report to their Directors of Pharmacies and are represented on the IRB, SRC, CLC, Audit Committee and DSMC.

During the clinical trial process, the research pharmacy checks that a participant is formally enrolled on the research protocol before dispensing investigational agents. The electronic Chemo Order Entry System (COE) is in place at MGH, BWH, DFCI and CHB. The system automatically checks subject registration and a protocol template is automatically provided when the physician begins writing the order for a protocol participant. These systems were created over ten years ago as a major move toward increasing patient safety and regulatory compliance.

2.2.2.13. Connell & O'Reilly Families Cell Manipulation Core Facility (CMCF) and DFCI Clinical Research Laboratory (CRL)

Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP) are monitored through the CMCF and CRL specific quality assurance standard operating procedures. These SOPs are maintained by the Quality Assurance Managers in the CMCF and CRL.

2.3. Protocol Specific Data and Safety Monitoring (Quality Control)

2.3.1. Overview

The Protocol Chair, as the sponsor, is responsible for developing a monitoring plan appropriate to the risk of the trial. The DF/HCC Lead Institution, as the Coordinating Center and designated trained monitor will implement monitoring activities ongoing to ensure that all sites are complying with regulatory and protocol requirements, data quality, and subject safety. Monitoring will occur before the clinical phase of the protocol begins and will continue during protocol performance through study completion.

2.3.2. Risk Categorization

Based on the complexity of the study design, study endpoints, clinical complexity and study population, geography, experience of the clinical investigator and of the sponsor with the investigator, data capture requirements, safety of the investigational product and stage of the study, the Protocol Chair, as sponsor determines the risk of the trial

A trial's risk category can be elevated, but can not be downgraded from these categories.

High Risk studies include:

- Trial for which a DF/HCC investigator holds the IND/IDE
- Investigator initiated Phase I and I-II trials
- Investigator initiated multi-center trials
- Investigator initiated interventional clinical trials using investigational agents/device
- Trials where DF/CHCC is manufacturing the study agent

Moderate risk studies include:

- Intervention trials sponsored by industry, national cooperative groups, NCI/NIH that include appropriate/approved data and safety monitoring plans
- Investigator initiated Phase II, II-III or III single institution studies that utilize only FDA approved agents/devices

Low risk studies include:

- Non-Intervention trials (including epi/obs/ outcomes/QOL/correlative lab/ancillary trials),
- Intervention trials that are Nutritional, Behavioral or Psychosocial
- Intervention trials that are diagnostic in nature

2.3.3. Monitoring Requirements

Monitoring plan requirements are based on the risk categorization of the trial.

High and Medium Risk Trials (PI-Initiated)

1. Pre-Study Investigator and Site Qualification Assessments

The research experience of all prospective investigators and the feasibility of the prospective site and their ability to comply with the Code of Federal Regulations (CFR) and Good Clinical Practice (GCP) is essential. The monitor is responsible for reviewing and documenting the experience of prospective investigators and the feasibility of prospective sites. The Protocol Chair, as Sponsor, is responsible for reviewing and assessing the site's feasibility to conduct and contribute to the goals of the trial.

2. Study Initiation Monitoring Assessment

Study Initiation Monitoring Visit (SIV) will be provided by the Protocol Chair, as Sponsor, to the clinical investigators and the investigative team for all participating sites. A monitor may be assigned to conduct the SIV. The SIV will provide the appropriate training and documents to conduct the study in accordance with the approved protocol, and with the applicable regulatory requirements, and to confirm the continued acceptability of the investigator to conduct the study.

3. Interim Monitoring Assessments

The Protocol Chair, as sponsor, or the designated monitors will conduct monitoring visits to ensure that participating site's clinical investigators and study team members are compliant with the protocol, regulations and institutional policies, 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 monitoring. Also, the participating site will be subject to on-site monitoring.

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

All data submitted to the QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The designated monitor and QACT Data Analysts assigned to the Protocol will perform the ongoing protocol data compliance monitoring with the support of the participating site's Coordinators and the Site Principal Investigators, and the Protocol Chair, as Sponsor.

An initial monitoring visit will be performed within 1 month of the first subject enrolling at each participating site.

Subsequent monitoring visits will be performed on a schedule according to the risk category of the trial. High Risk Studies will be monitored a minimum of every 3 months. Moderate Risk trials will be monitored every 6 months. A risk-based approach will be used by the monitor to determine the number of participant charts and which data elements will be monitored.

Following each monitoring visit, the monitor will communicate the monitoring findings and any additional requests in a follow-up letter sent via e-mail to the participating site's Site PI. The monitor will also complete a monitoring report to document the interim monitoring visit and forward it via e-mail to the Protocol Chair, as sponsor.

4. Close-Out Monitoring Assessments

The Close-out Monitoring Visit is usually conducted when all participants have completed the study, including treatment and follow-up assessments. At the Close-out monitoring assessment (visit), the monitor is responsible for ensuring that the investigator(s) 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(s) is aware of his continued obligations. The Close-out assessment visit is to finalize all the necessary procedures to conclude the clinical investigation at a specific investigator site.

Following the Close-out Monitoring Visit, the monitor will send a follow-up letter via email to the participating site's Site PI to conclude his/ her participation in the clinical study. The monitor will also complete a Close-out Monitoring Visit report to document the visit and forward it via e-mail to the Protocol Chair, as sponsor.

Low Risk Trials (PI-Initiated)

1. Pre-Study Investigator and Site Qualification Assessments

The research experience of all prospective investigators and the feasibility of the prospective site and their ability to comply with the Code of Federal Regulations (CFR) and Good Clinical Practice (GCP) is essential. The Protocol Chair, as Sponsor, is responsible for reviewing and assessing the site's feasibility to conduct and contribute to the goals of the trial.

2. Monitoring Assessments

The Protocol Chair, as sponsor, or designee is responsible to ensure that participating site's clinical investigators and study team members are compliant with the protocol, regulations and institutional policies, 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 monitoring. Also, the participating site will be subject to on-site monitoring.

An initial monitoring assessment will be performed within 1 month of the first subject enrolling at each participating site.

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

All data submitted to the QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Protocol Chair, as Sponsor, or designee and QACT Data Analysts assigned to the Protocol will perform the ongoing protocol data compliance monitoring with the support of the participating site's Coordinators and the Site Principal Investigators.

2.3.4. Escalation

The Protocol Chair, as sponsor, is required to provide oversight to ensure adequate protection of the rights, welfare and safety of study participants and the quality and integrity of the resulting data. In response to meeting this oversight role, designated trained 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 DFCI IRB as applicable and to the Quality Assurance Office for Clinical Trials, who evaluates the event and determines whether it needs internal escalation to a DF/HCC entity. 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.

2.4. Conflict of Interest

Faculty are responsible for following the Harvard Policy on Conflicts of Interest, as well as any Conflict of Interest policy established by their respective institution. They are required to disclose both to HMS and their own institution(s) the existence of any financial interests that could have real or apparent conflict with their research, regardless of the source of research funding. In addition, COI statements are required by DF/HCC for each protocol submission.

Conflicts of Interest for Investigators:

Each protocol application requires that every Investigator disclose the existence of any Conflict of Interest related to the research or the sponsor. A “Conflict of Interest” is defined as a Financial Interest held by the Investigator, his or her spouse, or dependent child that might affect or be affected by the research. This includes anything of monetary value, such as (1) salary or payments, (2) equity interests, and (3) intellectual property rights, with values that exceed certain *de minimis* values (\$10,000 per year in consulting income, or \$30,000 in equity in a publicly traded entity).

Investigators are also required to disclose any relationships with the trial sponsor, whether or not there is financial compensation involved. Investigators may not serve on the Board of Directors of a for-profit Business, and simultaneously participate in clinical research on a technology owned by that Business. This prohibition does not apply to non-profits. Investigators must be free of impermissible financial interests related to a relationship with the trial sponsor for a minimum of six months before participating in clinical research on a technology owned by the trial sponsor.

Dana-Farber Cancer Institute has entered into a Reciprocal Institutional Review Board Reliance Authorization Agreement with DF/HCC institutions, whereby it serves as the IRB of record for all cancer-related clinical trials requiring scientific review. Pursuant to this Agreement, DFCI is responsible for the initial review and identification of Conflicts of Interest in clinical trial protocols for all Investigators, regardless of institutional affiliation (the “Reviewing Institution”). When an Investigator indicates the existence of a financial interest as defined above, the relationship is evaluated by DFCI. If the Investigator is a DFCI faculty or research staff member, the appropriate strategies are implemented to manage, reduce, or eliminate the conflict, when possible. These measures may include, for example, disclosure of the financial interest in the informed consent form, the utilization of enhanced data safety oversight mechanisms, or independent data review and monitoring. If the Investigator is from an affiliated institution, DFCI notifies that appropriate official at Investigator’s Institution (the “Relying Institution”) of the existence of the COI and the recommended approach to management. Upon receiving the notification, the receiving Institution has the option to pursue a more stringent approach if its policy so requires.

The following statement appears on every IRB and SRC agenda regarding COI for IRB members:

CONFLICTS OF INTEREST FOR SRC/IRB MEMBERS: SRC/IRB members are required to recuse themselves from the discussion and vote on protocols where a conflicting interest exists, except to provide information at the SRC/IRB’s request prior to the deliberation and vote on the protocol. Please review the list of projects on the agenda with the issue of conflicts in mind and disclose any potential issue to the SRC/IRB chair in advance of the meeting when possible. The meeting minutes will document the recusal (i.e., the temporary absence of the SRC/IRB member during the deliberation and vote on the project with respect to

which the member has a conflict). A recused member will not count toward the quorum present for consideration of the project.

SRC/IRB members must recuse themselves from the discussion and vote on a protocol if they have a conflicting interest, which includes: (1) participation in the project; (2) a financial interest as defined below; and/or (3) any other examples referenced below. A conflict may arise because of an interest of the SRC/IRB member or his/her family; the aggregate interest of the SRC/IRB member and family is considered.

“Participation in the project,” for purposes of this policy, generally means the 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. “Participation in the project” excludes serving as a member of the SRC/IRB or the data monitoring board overseeing the project.

A financial interest is a “conflicting interest” under this policy, if it is one of the following interests in a business that is supporting or facilitating the project, or a business that is known to the SRC/IRB member to own (or have license rights to) the technology that the project is on: (a) receiving more than \$10,000 annually (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 (b) having an equity interest in a business, except for an interest of less than \$30,000 in a publicly held business. A conflicting financial interest also shall include having any ownership interest in a patent or a patent application covering the technology that the SRC/IRB member knows the project is on. A SRC/IRB member will not have a conflicting financial interest under this policy if the member has a financial interest that falls below the threshold in (a) or (b) and has no ownership interest in a patent as described above.

Other examples of conflicting interests include but are not limited to:

- serving as a board member (of a board of directors or scientific advisory board) or as an 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; or
- having certain non-financial interests that may raise a real or perceived conflict. These will depend on the circumstances. They may include, for example, having direct supervision over the investigator conducting the project, or participating in a separate project on technology that may directly compete with the technology in the project under review. Any real or perceived conflict, or a concern that there may be a real or perceived CONFLICT; that is not addressed above should be raised with the SRC/IRB chair. If the SRC/IRB chair determines there is a conflicting interest, then the member shall recuse himself or herself. The SRC/IRB chair reserves the right to request recusal as appropriate in any particular circumstances.”

All conflicts will be noted and recorded in the minutes of each meeting along with the above statement.

3. Plans for Assuring Data Accuracy and Protocol Compliance (Quality Assurance)

3.1. Internal Auditing

3.1.1. Overview

DF/HCC clinical trials are subject to internal auditing across all Disease Programs per the internal auditing policies and procedures. The DF/HCC Internal Audit Program has five full time auditors. All auditors report to the Quality Assurance Officer for DF/HCC to minimize the potential for institutional bias or conflict of interest inherent between clinical investigators and audit functions at the same institution.

Although all types of trials are audited, the main focus of the internal auditing program is the review of therapeutic PI-Initiated trials. Between 20% and 25% of accruing therapeutic PI-Initiated trials, which have a minimum of 5 subjects accrued, are audited per quarter. The auditors review from five to six records for each protocol. Participant's records audited may be from any of the DF/HCC affiliate hospitals. The auditing process for maintaining quality and improving the performance of clinical trials at DF/HCC is presented at regular education and training workshops organized by the Clinical Trials Education Office for both physicians and research staff.

3.1.2 Goals of Auditing Process

- To ensure and confirm ongoing clinical protocol compliance based on DF/HCC established guidelines, policies and procedures, and in accordance with federal regulations.
- To educate the clinical research staff to promote greater awareness and understanding of policies, procedures and objectives, and to increase efficiency and consistency in the clinical trial process at DF/HCC.
- To detect “system” errors in the DF/HCC policies and procedures that leads to non-compliance or risk to participants. This process allows corrective actions to be implemented in a consistent manner as well as meet changing needs across all participating institutions.

3.1.3 Audit Process

All active DF/HCC protocols are eligible for audit, including those protocols sponsored by NCI, pharmaceutical industry or other sponsors. The audit process begins with the selection of a protocol to audit. The internal Clinical Research Auditor selects protocols according to set criteria (i.e. disease site schedule, prioritization within the disease site, new investigators, and number of participants accrued). The auditor will inform the Overall and Site PIs and their appropriate study research staff of the protocol that will be audited at least one month in advance, and schedules the exit interview with the PI and his/her study team. Each PI to be audited will receive the following information:

- A letter listing the information that will be audited and the logistics of the day, such as time, date and place.
- A listing of the participants to be audited.
- A copy of the DF/HCC Clinical Trials Audit Manual

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 take into account the number of affiliate participants enrolled in the study and treatment arms.

The internal Clinical Research Auditor will complete an Audit Review Form for each participant during the audit to assess performance of data collection and protocol compliance. The selected participants' records, protocol regulatory documents and pharmacy records, if applicable will be reviewed. During an audit, physicians and/or clinical staff are available to assist the auditor as needed.

The auditor will summarize the results at the end of the audit and verbally communicate them to the study team. The exit interview will be conducted by the auditor with the Principal Investigator (PI) and the study staff and usually takes place within 72 hours of the audit completion. During the exit interview, the PI responds to any recommendations or questions that have arisen during the audit.

The internal Clinical Research Auditor will prepare a written final audit report within one week of the exit interview. The Overall PI will be asked to sign acceptance of the audit report and reply with corrective action plans as needed.

A major violation is generally defined as 1) An infringement, which significantly alters the clinical effectiveness of the treatment or the evaluation of its toxicity, 2) An infringement which violates Federal or DF/HCC requirements or policies or 3) Cumulative minor violations of the same nature. Minor violations are problems that occur when the protocol is not followed exactly, but the data are usable and valid or small deviations from Federal or DF/HCC policies.

The Audit Committee will review the audit reports at the next scheduled meeting to determine if any further action is required. No follow-up will be required if the audit is evaluated as Exceptional or Satisfactory. However, the Audit Committee will require follow-up if the audited protocol is evaluated to be Acceptable, Needs Follow-up or Unacceptable.

The audits are rated on the following performance scale.

- | | |
|-----------------|--|
| 1. Exceptional | Evidence of superior source documentation, data quality, protocol and regulatory compliance. No response required. |
| 2. Satisfactory | Few minor deviations noted. |

No response required.

- | | | |
|----|-----------------------------|--|
| 3. | Acceptable, needs follow-up | Requires follow-up for the major violation(s) |
| 4. | Unacceptable | Requires (at a minimum) a written corrective plan and interim re-audit with re-audit interval clearly specified in the audit report. |

Any major violation observed in a protocol audit is considered serious and requires corrective action or a written explanation from the Overall Principal Investigator. All audit results are maintained in the DF/HCC Audit Summary Database. This database is used to evaluate the program and as a continuous quality improvement tool.

Follow-up may involve implementation of new procedures regarding individual protocol performance or system-wide changes within DF/HCC. Other follow-up options may include a re-audit of the protocol in question, auditing a related protocol if the previously audited protocol is closed, or closure or temporary closure of the protocol are also follow-up options.

All audit results are maintained in the DF/HCC Audit Summary Database. This database is used to evaluate the program and as a continuous quality improvement tool. This information is presented to the Audit Committee and Clinical Investigations Leadership Committee members annually.

The reference manuals entitled *The Guide to Human Research Activities* and the *DF/HCC Audit Manual* describe the audit process and are readily available online on the CTEO and QACT websites.

3.2. Multi-center Trials: Auditing Participating Sites

External participating sites that are part of a DF/HCC initiated multicenter trial may be subject audits by the Quality Assurance Office for Clinical Trials Clinical Research Auditors, if requested and funding provided. Clinical Research Auditors may perform on-site audits at all external sites based on accrual, elapsed time, overall compliance for data submission or for cause as requested by any DF/HCC oversight committee, i.e. the IRB, DSMC, DSMB. The auditing process of the external sites is identical to that described in section 3.1.3 above.

3.3. Target Audits & Risk Assessment Process

In addition to the routine full scope audits conducted by the internal Clinical Research Auditors, the Quality Assurance Office for Clinical Trials (QACT) has added both Targeted Audits and Risk Assessments and Evaluations to the quality assurance repertoire.

Targeted Audits focus on review of a specific area of study conduct, i.e. Informed Consent, Adverse Events reporting, and Delegation of Authority. A Targeted Audit may be protocol specific or an assessment performed within a disease group or across the Consortium membership. One targeted audit is scheduled quarterly.

Risk Assessment and Evaluation provides a means for preemptively identifying weaknesses at any point in the research process at all levels. Risk Assessment and Evaluation focuses on the investigator and his or her study team to carry out their research safely and produce quality data. This type of evaluation focuses heavily on capacity and education. Primary attention is given to the number of studies an investigator is involved registered on and what responsibilities/risks have been assumed by taking on a given level of commitment. Staffing levels are evaluated in relation to the research burden of the investigator, i.e. are there enough qualified individuals involved to support the research effort. To ensure regulatory compliance at the Federal and Institution level, education and awareness of roles and responsibilities on the part of the investigator and study staff are also evaluated. Risk Assessment and Evaluations are performed at the request of a Disease Program, ancillary group or other intuitional oversight committee.

3.4. Escalation

If an audit is evaluated as “Unacceptable”, the Clinical Research Auditor must notify the voting members of the Audit Committee, the DF/HCC Medical Director for Clinical Trials Operations and the DF/HCC Associate Director for Administration of the violations within 48 hours of the exit interview. The notified members must review the major violations and inform the Clinical Research Auditor 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 (with the PI’s Division Chief cc’ed) 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 Clinical Research Auditor must notify the voting members of the Audit Committee and the DF/HCC Medical Director for Clinical Trials Operations 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 deficient audit.

If protocol suspension is deemed necessary, the Chair of the DF/HCC Audit Committee or designated member would contact the PI, Director of OHRS and those responsible for oversight of the PI of the protocol within 24 hours of the audit finding notification via the phone. These phone conversations must then be documented and given to the Clinical Research Auditor via an email or memo. The Director of OHRS will notify the IRB chairs and will take steps to amend the protocol tracking system and the Oncology Protocol System

to reflect the closure. A protocol, which has had accrual suspended because of any serious or continuing non-compliance and has harmed subjects as determined by the IRB, will be reported to the US DHHS Office for Human Research Protections (OHRP) and the FDA, if appropriate. The Director of the OHRS will notify OHRP in writing within 30 days of the IRB's decision if the serious and continuing non-compliance meets the threshold for a report as set forth in the OHRS policy.

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

All protocols deemed “Unacceptable” or requiring immediate action will be followed up with a complete audit report review and protocol status update 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 Clinical Investigations Leadership Committee (CLC) for review.

Any protocol closed by the Audit Committee can only be reopened after the Audit Committee and the DFCI 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 of committee raised by the multiple unacceptable audits.

Appeals Process

The standard process for an audit review is at the monthly Audit Committee meeting, where the formal PI written response and audit findings are assessed.

In cases where the PI feels that the audit was inaccurate or unfair and wishes to appeal, the PI of an audited study may request to be present during the Audit Committee’s review of the audit. The PI must notify the Clinical Research Auditor 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.

At the open session of the Audit Committee review, the PI will have the opportunity to present and discuss their concerns with the committee members. During the 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. The PI will be notified of the Audit Committee’s decision within 24 hours of the meeting.

In the event the PI feels the issues have not been addressed adequately, the appeal will progress to the DF/HCC Medical Director for Clinical Trials Operations and the DF/HCC Associate Director for Administration. The PI must notify the Clinical Research Auditor 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 Medical Director for Clinical Trials Operations and the DF/HCC Associate Director for Administration. The DF/HCC Medical Director for Clinical Trials Operations 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 will make a final determination. The PI will be notified the decision within 24 hours of the meeting.

4. Assuring Compliance with Requirements for Adverse Event Reporting

4.1. Overview

All protocols are required to have a protocol section describing the adverse event reporting. The Overall or Site Principal Investigator (PI) must report all significant serious adverse events (SAE) for drugs, biologics, procedures or devices to the DFCI Institutional Review Board (IRB), to the protocol sponsor (including the NCI Program Director) and, when applicable, to national chairs of multi-center/group studies, Institutional Bio-safety Committees, FDA and NIH/OBA (Office of Biotechnology Activities). The treating physician is responsible for notifying the Overall PI of the incident. Copies of all reports must be submitted to the Office of Human Research Studies (OHRS). They will then be forwarded for IRB review. For studies that require a report to be filed with other agencies (study sponsor, FDA, NIH/OBA, Institutional Biosafety Committees, etc.) submission to the OHRS does not substitute for a report from the overall Principal Investigator to these agencies.

4.2. DFCI IRB Requirements and Reporting

Serious Adverse Events (SAE) are to be submitted to the DFCI IRB on the SAE Reporting Form. This form must be submitted in addition to any sponsor/company or other forms except where AdEERS is used. When an SAE occurs involving a participant being treated or followed by a physician outside DF/HCC and there is a time requirement involved, all reporting should take place within the 10 working days based on a start date of the time of notification to the overall PI. It is required that the PI or designee keeps a copy of all submitted SAE reports in the study files. Unanticipated Problems that do not meet the SAE reporting requirements are submitted to the DFCI IRB using the Unanticipated Problem Form.

The IRB is responsible for determining whether a reported event rises to the level of an unanticipated problem involving risks to subjects or others. OHRS is responsible for reporting these determinations to the appropriate government office(s) {21 CFR 56-108 (b) (1) and 45 CFR 46}.

DFCI IRB Reporting Forms

When reporting adverse events to the DFCI IRB, one of the following forms MUST be used.

1. Serious Adverse Event Reporting Form:

http://www.dfhcc.harvard.edu/fileadmin/DFHCC_Admin/Clinical_Trials/OPRS/Forms_Instructions/Post_Activation/SAE_Reporting.doc

The SAE Reporting Form must be used to report SAEs experienced by DF/HCC participants enrolled in a DF/HCC study including any serious adverse events on DF/HCC led Multi-Center trials where the event occurs at a non-DF/HCC site.

Full written SAE report must be submitted to OHRS as soon as possible, but no later than **10 working days** from notification of event. All reports must be submitted via OHRS Submit.

a. Follow Up SAE Reports:

When submitting follow up reports to previously reported SAEs, attach a copy of the original report and any prior IRB determinations to the follow up report. This gives the reviewer all the information required to conduct a thorough review and eliminates questions that might otherwise be raised.

2. AdEERS Reporting Form:

[https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)

The NCI AdEERS form may be used in place of the DFCI IRB SAE Reporting Form for NCI or Cooperative Group studies only. AdEERS reports must be submitted to OHRS as soon as possible, but no later than 10 working days from notification of event. All reports must be submitted via OHRS Submit.

If the PI determines that the adverse event warrants a change to the protocol and/or consent form document(s) the completed AdEERS report must be submitted via OHRS Submit along with an amendment form. The AdEERS report must be attached to the amendment form as supporting documentation for the IRB to review.

a. Follow Up AdEERS Reports:

When submitting follow up reports to previously reported AdEERS, attach a copy of the original report and any prior IRB determinations to the follow up report. This gives the reviewer all the information required to conduct a thorough review and eliminates questions that might otherwise be raised.

4.3. IND/IDE Safety Reports

The DFCI IRB policy regarding the receipt and review of IND/IDE safety reports is in line with guidance issued by the Office for Human Research Protections in September 2003 and by the Food and Drug Administration in January of 2009. As of March 1, 2009, the DFCI IRB will not accept IND/IDE Safety Reports reporting events that take place outside of the DF/HCC by outside sponsors unless the event is determined by the Overall PI to be:

1. Serious or Life-Threatening; **and**
2. Unexpected; **and**
3. Related to the Research Intervention; **and**

4. **Has an implication for the conduct of the study you are conducting 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.)

Responsibility of Principal Investigator

It is the responsibility of the Principal Investigator to review all IND/IDE safety reports provided by an outside sponsor (or themselves if they are the sponsor) **within 60 days of receipt** and determine that indeed the four criteria above DO NOT APPLY.

Any sponsor correspondence requiring immediate action as a result 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 OHRS **within 10 days of receipt**.

If the IND/IDE safety report **does meet** all of the criteria noted above, the Principal Investigator must submit the IND/IDE safety report to the IRB via the amendment form **within 90 days from original date of receipt** including any applicable changes to the protocol and/or consent form.

The continuing review form includes a requirement that Principal Investigators attest to the review of all IND/IDE safety reports that have been issued during the year but not submitted to the IRB because they do not meet the outlined criteria above.

4.4. Adverse Event Reporting Guidelines for DF/HCC

The DFCI IRB requires the following events be reported:

- **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 protocol as not requiring reporting.
- **ALL Grade 5 (fatal) Events** – When subject is enrolled and actively participating in the trial OR when event occurs within 30 days of the last study intervention.

Notes:

- If subject is in Long Term Follow Up, death is reported at continuing review.

Other Reporting Requirements:

PI-Initiated/Sponsor holds IND

The sponsor-investigator, as the holder of the IND/IDE, is responsible for reporting serious adverse events directly to the FDA. In addition to the FDA Form #3500a (Mandatory Medwatch Form), the DF/HCC Overall PI may also be required to complete a form supplied by the sponsor. The DFCI IRB reporting requirements may differ from the sponsors. DF/HCC investigators must comply with both.

Industry Sponsored (Investigational)

In addition to the DFCI IRB SAE reporting form, the DF/HCC PI may also be required to complete a form supplied by the sponsor. The DFCI IRB reporting requirements may differ from the sponsor. DF/HCC investigators must comply with both.

Industry Sponsored (Commercial)

The FDA's MedWatch Online form, #3500, 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. The sponsor of the trial, however, may have its own form.

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

The following must be reported:

- (1) Any SAE that is both unexpected and associated with the use of the gene transfer product
- (2) Any new finding from animal testing that presents a significant risk for human research.

Reports must be sent:

- (1) Within 15 days if unexpected and associated;
- (2) Within 7 days if fatal or life-threatening, unexpected and associated;
- (3) Follow-ups for previously reported events must be sent no later than 15 days of receipt by the investigator/sponsor;
- (4) Any event that occurs after the end of a trial and is associated with the use of the gene transfer product must be reported within 15 days of the determination; and
- (5) Any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity must be reported as soon as possible, but no later than 15 days after the sponsor's initial receipt of the information. Submit the appropriate IRB form to the following: Institutional Biosafety Officer, sponsor, if applicable (may have own reporting form) FDA (if Serious and Unexpected, or death) and NIH/OBA

The PI is responsible for reporting all applicable adverse events to NIH/OBA. Under the NIH Guidelines for Research Involving Recombinant DNA Molecules, a PI may delegate the reporting responsibilities set forth in Appendix M-I-C to another party (i.e., the sponsor), with written notification of the delegation to OBA. The protocol document should outline the reporting policy.

Additional information about Human Gene-Transfer Reporting requirements can be found in section 25.9 of The Guide to Human Research Activities (Revised August 2009).

4.5. Definitions

Adverse Event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable or definite). (NIH Guidelines, January 2001)

Serious Adverse Event: Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, and persistent or significant disability/incapacity, or a congenital anomaly/birth defect. 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 appropriate 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)

Life-threatening Adverse Event: Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death (21CFR312.32a)

Unexpected Adverse Event (FDA definition): Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure 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 current application, as amended. “Unexpected” as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product (21CFR312.32a)

Unexpected Adverse Event (NCI definition): Any adverse event which is not listed in the NCI Agent Specific Expected Adverse Event List. This list is updated electronically in real time.

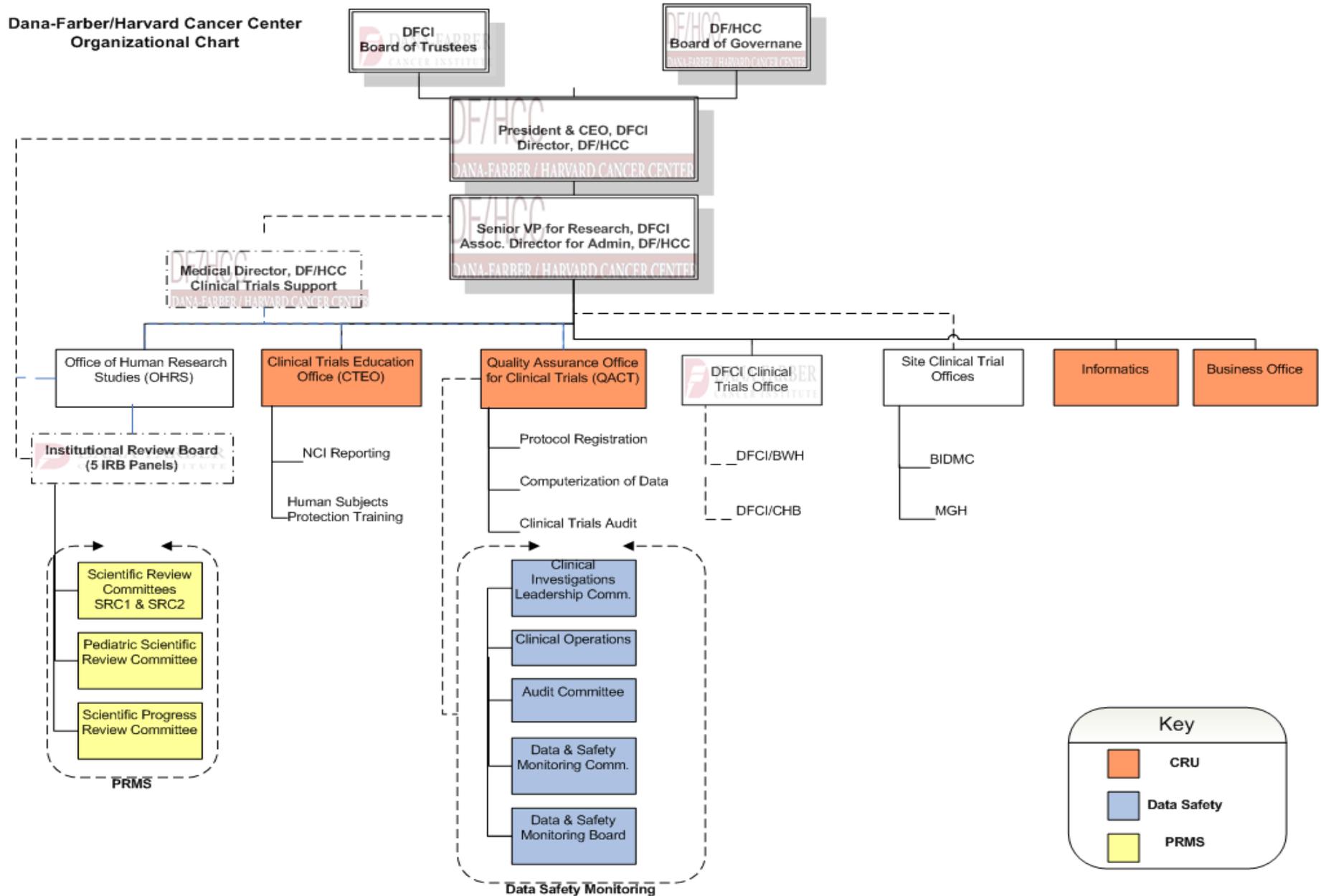
Attribution: The determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories:

- Definite: The adverse event is clearly related to the investigational agent(s), device(s) or procedure(s).
- Probable: The adverse event is likely related to the investigational agent(s), device(s) or procedure(s).
- Possible: The adverse event may be related to the investigational agent(s), device(s) or procedure(s).
- Unlikely: The adverse event is doubtfully related to the investigational agent(s), device(s) or procedure(s).
- Unrelated: The adverse event is clearly NOT related to the investigational agent(s), device(s) or procedure(s).

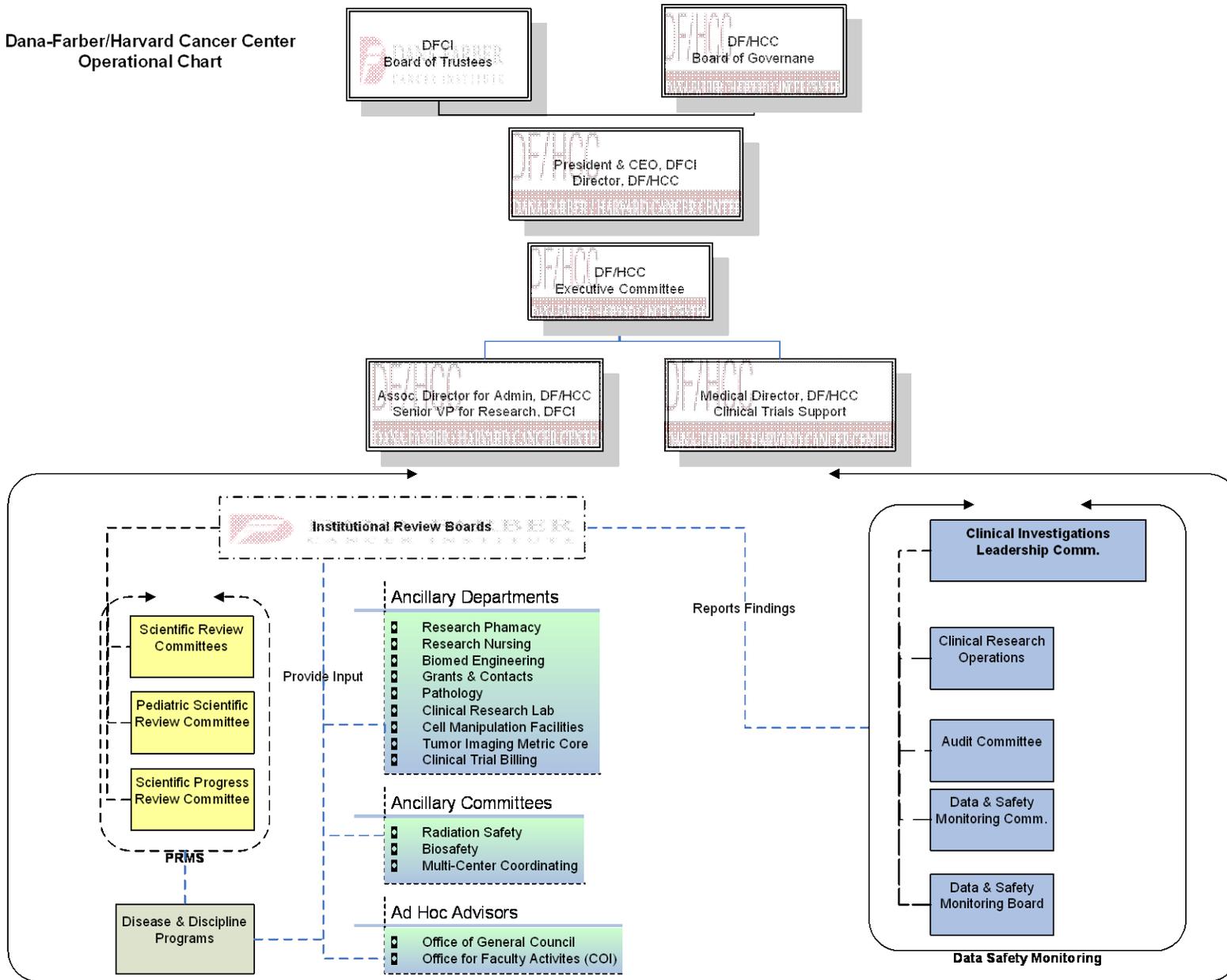
5. Process for Assuring that any Action resulting in Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant

All temporary or permanent closure determinations made by the IRB or DF/HCC due to non-compliance or safety concerns will be reported by OHRS 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.

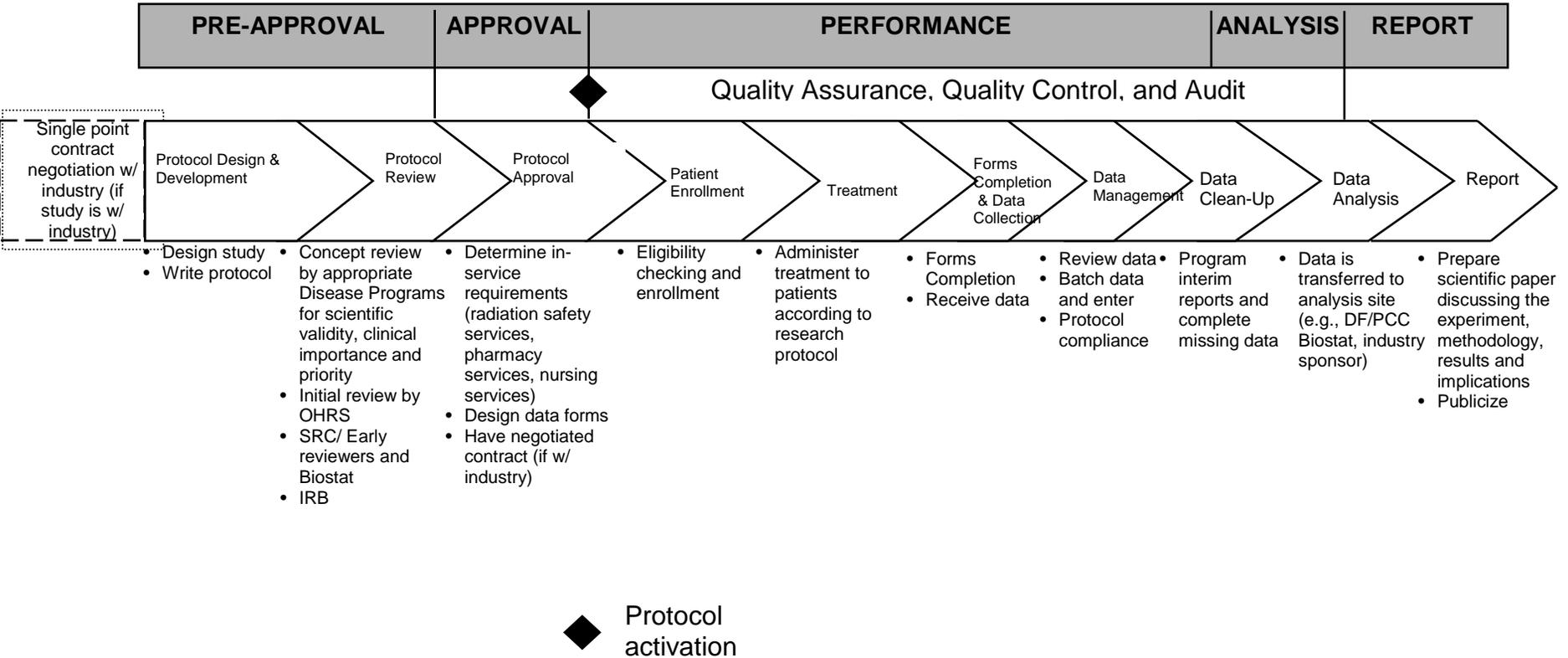
Dana-Farber/Harvard Cancer Center
Data and Safety Monitoring Plan



Dana-Farber/Harvard Cancer Center
Operational Chart



Dana-Farber/Harvard Cancer Center *Clinical Trials Process*

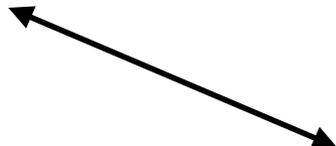
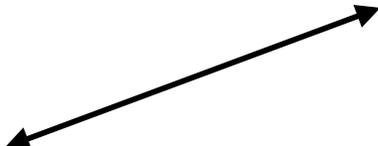


Note: Detailed process steps may vary according to specific study and funding source

STUDY TEAM

SITE PRINCIPAL INVESTIGATOR

- Responsible for conduct of trial at their institution, including data management/ collection
- Collaborates with Overall P.I. on conduct of trial



BIostatistician

- Early protocol review
- Prepares statistical section
- Interim analysis
- Data Collection Forms design

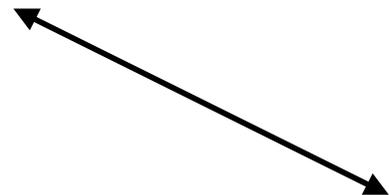


OVERALL PRINCIPAL INVESTIGATOR

- Protocol Development
- Overall responsibility for conduct of the study
- Data Collection Forms design
- Oversees Data Manager

CLINICAL RESEARCH COORDINATOR (CRC)/ASSOCIATE (CRA) /RESEARCH NURSE

- Data Collection Forms design
- Confirms eligibility and signed consent
- Registers patients with the QACT
- Ensures protocol compliance for required data
- Coordinates general management of study



DATA ANALYST

- Early protocol review
- Data Collection Forms design
- Set up and maintain computerized database
- Creates and distributes data query reports
- Prepares data for statistical analysis

