

Section 20: Protocol Submission, Review and Activation

DF/HCC requires a detailed review of all trials. This section describes the protocol review process (from concept to closure) and briefly discusses the roles of the offices and committees involved in the reviews.

20.1 The Review Process

IRB review is required for:

- Research projects that involve human participants and that are conducted by students, faculty members, or DFCI staff
- Oncology research projects that involve human participants and that are conducted by students, faculty members, or staff of DF/PCC and/or DF/HCC institutions:
 - BIDMC
 - BWH
 - Children's Hospital Boston
 - DF/PCC Network Affiliates (using DFCI as IRB of record)
 - MGH
 - Harvard Medical School
 - Harvard School of Public Health

20.2 Submitting a Trial for Review

Submissions should be sent to the OHRS at:

Sender originating from DFCI:

Dana-Farber Cancer Institute
20 Overland St.
2nd Floor

OR

Sender *not* originating from DFCI :

Dana-Farber Cancer Institute
44 Binney Street
OS229
Boston, MA 02115

The review process begins when the OHRS receives the complete submission package.

Incomplete submissions will *not* be placed on the agenda for the next meeting. Therefore, investigators should review the instructions on the application forms for each type of submission. Submission forms are available on the OHRS website.

20.3 Basic Elements of an IRB Submission

New Project Application Form

The application form must be completely filled out. Signatures are required from the investigator, site-responsible investigator, members of the research team and the Disease Program Leader.

The Disease or Discipline-based Program Leader is a DF/HCC position that oversees the functions of a specific disease or discipline-based program. The Program Leader or designee is required to sign off on all new protocol submissions. This signature implies that the leader has reviewed the protocol with the appropriate Program members and the decision has been made that the protocol fits into the priorities of the overall research plan for the program. The program serves an integral role in the design, development and prioritization of research activities.

Informed Consent Form (and Assent Form, if Applicable)

The required template and IRB-required and suggested language for consent forms are available on the OHRS website.

Research Protocol

A detailed research protocol is required for IRB review of your research. Guidelines for writing greater than minimal risk protocols and behavioral and social protocols are available on the OHRS website and in the DF/HCC Clinical Investigator Toolkit.

Priority Lists

The protocol priority lists outline available protocols for participants with a given disease. The listing includes pending, active, and closed protocols. They are available for distinct disease programs (e.g., breast) and are broken down by site and extent of disease. Each program is responsible for prioritizing protocols within their specific area. Protocols must be prioritized within the appropriate category prior to submission to the IRB.

Protocols are prioritized to ensure the efficient completion of trials. It is designed to minimize competing protocols and to effectively utilize the resources that manage the clinical trial process, including central core facilities, participants, and staff.

Priority lists for adult and pediatric protocols are available via OncPro.

Grant Proposals

Trials that will or may be funded by a grant must include a copy of the grant for IRB review. To perform a complete review, the IRB is required to examine the grant proposal. Investigators need not include the funding section or the breakdown of dispersal of funds unless requested by the IRB.

Recruitment Material (Advertisements, Posters, Flyers, Press Releases, etc.)

The IRB reviews any advertisements, flyers, and Internet postings for participant recruitment, as well as

correspondence to participants prior to its use. NCI's Physician Data Query (PDQ) postings do not need to be submitted for IRB review and approval.

All recruitment materials must be submitted with the initial application. Advertisements, press releases, etc. may qualify for expedited review.

Surveys and Questionnaires

The IRB reviews all research instruments such as surveys or questionnaires. All instruments must be submitted with the initial project application.

Investigator Brochure, Device Specifications, and Package Inserts

The IRB is required to examine the investigator brochure (known as IB) and/or device manual in order to adequately assess the risk/benefit ratio for participants participating in the research. When approved drugs or devices are being used, a copy of the package insert should be submitted with the application materials. During the conduct of the trial, all updates to these manuals must be sent to the IRB and the Research Pharmacy.

Conflicts of Interest

The IRB requires that investigators submit conflict of interest information on a trial-by-trial basis. This information is requested on each new protocol application form and asks that investigators indicate any conflicts of interest that they may have. In situations where an investigator may have potential financial conflicts of interest, the IRB may ask the investigator to explain how the potential conflict of interest will be minimized or resolved and may require disclosure of conflicts of interest in consent forms. The IRB may also request input from the Conflict of Interest (COI) Officials for managing individual conflicts of interest.

Data and Safety Monitoring Plan (DSMP)

A data and safety monitoring plan may incorporate many different methods of monitoring. The [DF/HCC Data and Safety Monitoring Plan](#) describes how we monitor protocols. A Data Safety Monitoring Board (DSMB) must review all phase III protocols. DF/HCC has a central DSMB that must be used for all PI-initiated protocols. The DF/HCC Data Safety Monitoring Committee (DSMC) reviews high Risk, PI-initiated Phase I and II trials. High risk is defined as any of the following: the first time in humans, the first time in children, gene transfer, or multi-center. These DF/HCC committees may also review other protocols that do not have an outside committee reviewing them.

FDA Correspondence

Studies involving the use of any investigational or unlicensed test article must include copies of all relevant correspondence between the sponsor and the FDA. Relevant correspondence would include:

- documentation of the FDA assigned IND/IDE number for the proposed research
- confirmation of an FDA granted exemption

20.4 Other Documents that May Be Required

Prior to trial activation, there are several documents that may be required by trial sponsors. These are outlined below.

FDA Form 1572

This form is a component of an IND application. It provides the name and address of the institution where the clinical investigation will be conducted, the names of the PI and all other sub-investigators, and other pertinent trial information.

The FDA Form 1572 outlines the duties and obligations of investigators. It is imperative that all investigators read it. The overall investigator within the DF/HCC is the only one required to sign the 1572, committing to all the rules and regulations set by the FDA for conducting clinical trials. The site PI should not sign in addition. Curriculum vitae (CV) are required for the PI and for all other investigators as evidence that they are “qualified as an expert in the clinical use of the drug under investigation.” The completed form is submitted to the sponsor, who then incorporates the information into an IND application.

For trials sponsored by the NCI, the QACT and/or CTEO will contact investigators once a year for updated information for each NCI-specific 1572. These 1572s must be submitted to NCI by August 1 of each year. Investigators must also provide to NCI an updated, signed, and dated CV as a part of this annual investigator registration process.

Letter of Assurance from the IRB

Many pharmaceutical sponsors will request a roster of the IRB members. The OHRS does not provide this list. Instead, the OHRS provides a letter stating that the Institute is in compliance with all Massachusetts, HHS, and FDA regulations governing research on human participants. This letter also provides an Assurance Project Number on file with the federal government through the federal Office for Human Research Protections (OHRP). This “sponsor” letter is available on the OHRS website and the DF/HCC Clinical Research Unit (CRU) website.

Laboratory Normal Value and Letter of Certification

Sponsors require evidence that the Clinical Laboratory Improvement Amendments (CLIA) certifies every laboratory monitoring the health of study participants. The laboratory values are used to assess toxicity and changes in laboratory values while the participant is enrolled in the trial. At DF/HCC, this information can be obtained from the various administrative directors of laboratories offices or the [DF/HCC Clinical Research Unit website](#) under “Regulatory Documents.” The Certificate of Pathology (CAP) for DF/HCC institutions is also included in the CLIA certificate. When laboratories outside the DF/HCC are used, the PI or the PI’s designee must contact them as the same information must be obtained and submitted to the trial sponsor. Laboratories used to process research samples only, who not to diagnose or treat patients, are not required to be CLIA-certified.

Clinical Trials Agreement

There is a legal contract between DF/HCC and the pharmaceutical sponsor. The clinical trial agreement is developed by research administration with input from DF/PCC, BIDMC, and CHB legal staff. The

agreement includes the budget for the trial. The administrator from each division will assist investigators with actual budgets. Confidential clinical trials agreements are the property of the Institute and the investigator and will not be kept with the investigator's trial binder.

IRB-approved Informed Consent

Pharmaceutical sponsors require receipt of the IRB-approved consent form prior to enrollment of the first participant. The OHRS recommends that consent documents be sent to the sponsor after IRB approval but prior to trial activation. Any changes requested by the sponsor must be reviewed and approved by the IRB. The study team must maintain copies of the approved consent documents in their trial files.

Investigator Financial Disclosure Form

All individuals listed on the 1572 are required by the pharmaceutical company sponsoring the trial to complete an investigator financial disclosure form. The form seeks to identify any significant equity, proprietary, or financial interest those participating in the trial may have in the company.

20.5 The Review Committees

Scientific Review Committee (SRC)

As an NCI-designated comprehensive cancer center, DF/HCC is required to conduct a review of scientific merit for each research trial it reviews. To comply with the NCI requirement, and to assist the IRB panels in their review, the SRC focuses on scientific merit, scientific priorities, and the scientific progress of the clinical research protocols of the cancer center. The SRC meets weekly.

The voting members of the SRC include the scientific chair, physicians, and biostatisticians. Additionally representatives from QACT, pharmacy, and nursing departments provide input for SRC consideration.

Two physicians are assigned as the lead reviewers on each protocol. The primary and secondary reviewers are responsible for the thorough review of each protocol. These reviewers take the lead in the discussion of assigned projects. The entire SRC reviews and discusses all new protocols. Reviewer assignments are made by the OHRS.

All SRC deferrals must be sent back to the full committee for re-review. Protocols are not sent to the IRB until the determination has been made that the investigator has adequately responded to all conditions identified by the SRC.

Pediatric Scientific Review Committee (PSRC)

The PSRC reviews all greater than minimal risk trials involving pediatric patients and ensures that the protocol is of appropriate scientific and therapeutic merit and is in accordance with the mission of the DFCI. All investigators from the department of pediatric oncology at DFCI must submit protocols to the PSRC for review and approval.

The committee chairperson appoints committee membership. Voting membership includes a representative from the major disciplines and includes physicians and biostatisticians. Additionally representatives from QACT, pharmacy, and nursing departments also attend to provide input for PSRC

consideration.

Institutional Review Board (IRB) Review Committees

DF/HCC has six fully functioning and federally registered IRB panels. Each one is made up of at least five members. At least two are licensed physicians, one a non-scientist, and one a member who is not otherwise affiliated with the Institute.

While any IRB panel may review any protocol in any stage of the review and approval process, including amendments and deviations, the IRB panels generally review protocols as follows:

IRB Panels A and B

Panels A and B primarily review new protocols, as well as any changes to approved protocols (i.e., amendments). These boards each meet twice monthly. Panel A meets on the first and third Tuesday of the month, and Panel B meets on the second and fourth Tuesday of the month.

IRB Panels C and F

Panels C and F primarily review serious adverse events (SAEs) that occur while participants are participating in a research trial, as well as the continuing review of previously approved protocols. All approved protocols are required to be reviewed in a “substantive and meaningful” way at least annually. These panels each meet twice monthly. Panels C and F meet on alternating Thursdays.

IRB Panel D (Non-therapeutic Studies)

Panel D reviews all (both adult and pediatric) social and behavioral research and protocols involving additional procedures such as blood draws or bone marrow aspirates. IRB D also reviews tissue repository research, studies involving questionnaires, epidemiological trials, genetic testing, and counseling trials. Panel D meets on the second and fourth Monday of the month.

IRB Panel E

IRB Panel E reviews research or research related events that require an urgent or speedy resolution. This includes, for example, single patient INDs, local adverse events or other protocol-related events.

20.6 Description of Protocol Reviewers

The following departments play a crucial role in the review of new and ongoing research.

REVIEWER	PURPOSE
Pharmacy Department	Considers the availability and dispensing issues relative to the drug proposed for the trial and the accuracy of the protocol relating to pharmacy issues.
Nursing Department	Reviews the clarity of the treatment plans and considers how the trial will affect staffing and training.
Quality Assurance Office for Clinical Trials (QACT)	Considers the proper registration process for the trial and verifies that the document includes the essential elements for managing the trial. The QACT also considers future forms development for computer entry.
Research Administration, Including Legal Consultation	Considers the protocol from a contractual perspective; this includes negotiating with pharmaceutical companies and getting grants and funding sources. This process also includes a review of the document from a legal standpoint.
Office for Human Research Studies (OHRS)	Conducts pre-reviews of new project application submissions and the informed consent document.

20.7 Review and Approval of Other DF/HCC Departments/Committees

Departments/Committees with review responsibilities include but are not limited to:

- Biomedical Engineering
- Biosafety Officers and/or DFCI Institutional Biosafety Committee (IBC) and Harvard Committee on Microbiological Safety (COMS)
- Radiation Safety Officers and/or Radiation Safety Committees
- Cell Manipulation Core Facility
- Tumor Imaging Metrics Core
- Clinical Research Lab
- Pathology Department
- Clinical Trials Billing Department

The OHRS assists in the coordination of review with these departments and/or committees. Investigators will be informed of other review requirements upon receipt of the review from the SRC or PSRC. Studies conducted at MGH, regardless of which DF/HCC site is the lead, may require review by the MGH Pathology department, IBC and Radiation Safety Committee. These reviews are coordinated by the MGH Cancer Center Protocol Office and do not require a separate submission by the research team.

No project may be activated until all relevant committees have granted approval.

20.8 Notification of Board Actions

OHRS will communicate the results of a review to the investigator and designated member(s) of the study team as soon as practical. Investigators are asked to respond to questions or requested revisions to a trial or trial materials as soon as possible. Responses should be made *within 30 days of the review letter*.

In cases where the IRB concerns are related to subject safety on an active trial, investigators may be expected to respond in a much shorter time frame. Any such expectations will be communicated to the investigator and study team.

20.9 Review Outcomes

The review committees may make one of the following determinations as a result of their review of research submitted for initial review or for continuing review:

1. **Approve:** The protocol and accompanying documents are approved as submitted. Final approval will commence on the day the trial is approved by an action of the convened IRB or chairperson or designee and expire within one year of the meeting date but not later than the day preceding the date of review.

During initial review, participants may not be recruited into the trial until final approval has been issued, administrative requirements are satisfied, and the protocol has been activated. Protocol revisions may not be initiated until final approval has been issued.

The conditions for continued approval, and the time frame (if any) within which they must be met, will be stated in the approval letter. If the conditions are not met, approval may be withdrawn.

2. **Require Modifications (Conditional Approval):** A vote of conditional approval is granted only when the committee finds that the required revisions are minor and need only to be incorporated into the protocol and/or consent document or if the required changes or information requested meet the criteria for expedited review. For example, this might be adding appropriate study staff, editing the consent form for clarity (but does not include adding information about risks to participants or about costs to participants); adding additional blood collection or other biological collection as outlined in the allowable categories for expedited review.

A member of the IRB confirms responses to conditional approvals.

Any uncertainty or question about the investigator's response will be referred to the full committee for additional review.

3. **Defer:** Protocols are deferred when significant questions are raised during the review requiring its reconsideration after additional information is received from the investigator and/or sponsor. The investigator will be informed in writing of the required changes and requested information and must provide the IRB with the changes or information, or an explanation of why these changes

are not necessary.

4. **Disapprove:** A protocol may be disapproved where it fails to meet one or more of the criteria used by the IRB for approval of research. The investigator will be given a detailed communication describing the issues related to this disapproval. The investigator is allowed to respond to the IRB in person or in writing regarding this decision.

Disapproval cannot be given through the expedited review mechanism and may only be given by majority vote at a convened meeting of the IRB. If the IRB disapproves a trial, no other review body or person may grant approval.

5. **Table:** The IRB may table a review due to inadequate time or members present to conduct a thorough review. In this case, the investigator will be notified and the review will be rescheduled for another meeting.

20.10 Response to Committee Requests

The SRC and IRB require a response from investigators, in a point-by-point manner, preferably *as soon as possible*.

Any revisions required by a review committee must be incorporated into the documents as described in the decision memo. Disagreements with a decision or specific requirements should be documented and explained in the response memo. Investigators have the right to discuss IRB requests for revision and decisions of disapproval directly with the committee. The IRB, however, retains the final authority for approval of proposed research with human participants.

The IRB review process allows investigators various levels of appeal from the time a trial receives initial review through approval or disapproval. Any and all IRB decisions are contingent upon the response of the investigator. If the IRB finds that the negotiation is at an impasse, the IRB may request an intramural and/or extramural independent consultant review. The IRB wishes to respect the investigators' intellectual property; therefore, prior to assigning a consultant, investigators are asked if there is anyone they would *not* like to review their trial.

20.11 Claim of Exemption

The DFCI IRB and DF/HCC require that investigators submit studies for confirmation of Exemption from IRB review pursuant to the regulations found at [45 CFR 46.101\(b\)](#) and [21 CFR 56.104](#).

Investigators are required to submit documentation on the "Request for Exemption or Determination That Activity Is Not Human Subject Research" form, which is available on the OHRS website. This allows a pre-submission consultation with the investigator.

The DFCI IRB will consider the following types of research exempt from IRB review. Exemptions will not be granted to the following types of research when the study population includes prisoners.

Classifications of Exemption

- (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices. This includes research on regular and special education instructional strategies, research on the effectiveness of or the comparison among instructional techniques,

curricula, or classroom management methods.

This *does not apply* to research that is regulated by the FDA.

- (2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
- a. Information obtained is recorded in such a manner that human participants can be identified, directly or through identifiers linked to the participants; and
 - b. Any disclosure of the human participants' responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation.

This *does not apply* to research that is regulated by the FDA.

- (3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt, if:
- a. The participants are elected or appointed public officials or candidates for public office; or
 - b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

This exemption *does not apply* to children (anyone less than 18 years of age), except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

This *does not apply* to research that is regulated by the FDA.

- (4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that participants cannot be identified, directly or through identifiers linked to the participants.

The IRB defines subjects who cannot be identified, directly or through identifiers linked to the participants' as cases when the investigator has documented that he or she cannot and will not have access to the sources of these data or specimens then they are anonymous to the investigator. This attestation will be collected from investigators. Such materials must already exist at the time the research is proposed.

This *does not apply* to research that is regulated by the FDA

- (5) Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:
- a. Public benefit or service programs;
 - b. Procedures for obtaining benefits or services under those programs;
 - c. Possible changes in or alternatives to those programs or procedures; or
 - d. Possible changes in methods or levels of payment for benefits or services under those programs.

This *does not apply* to research that is regulated by the FDA.

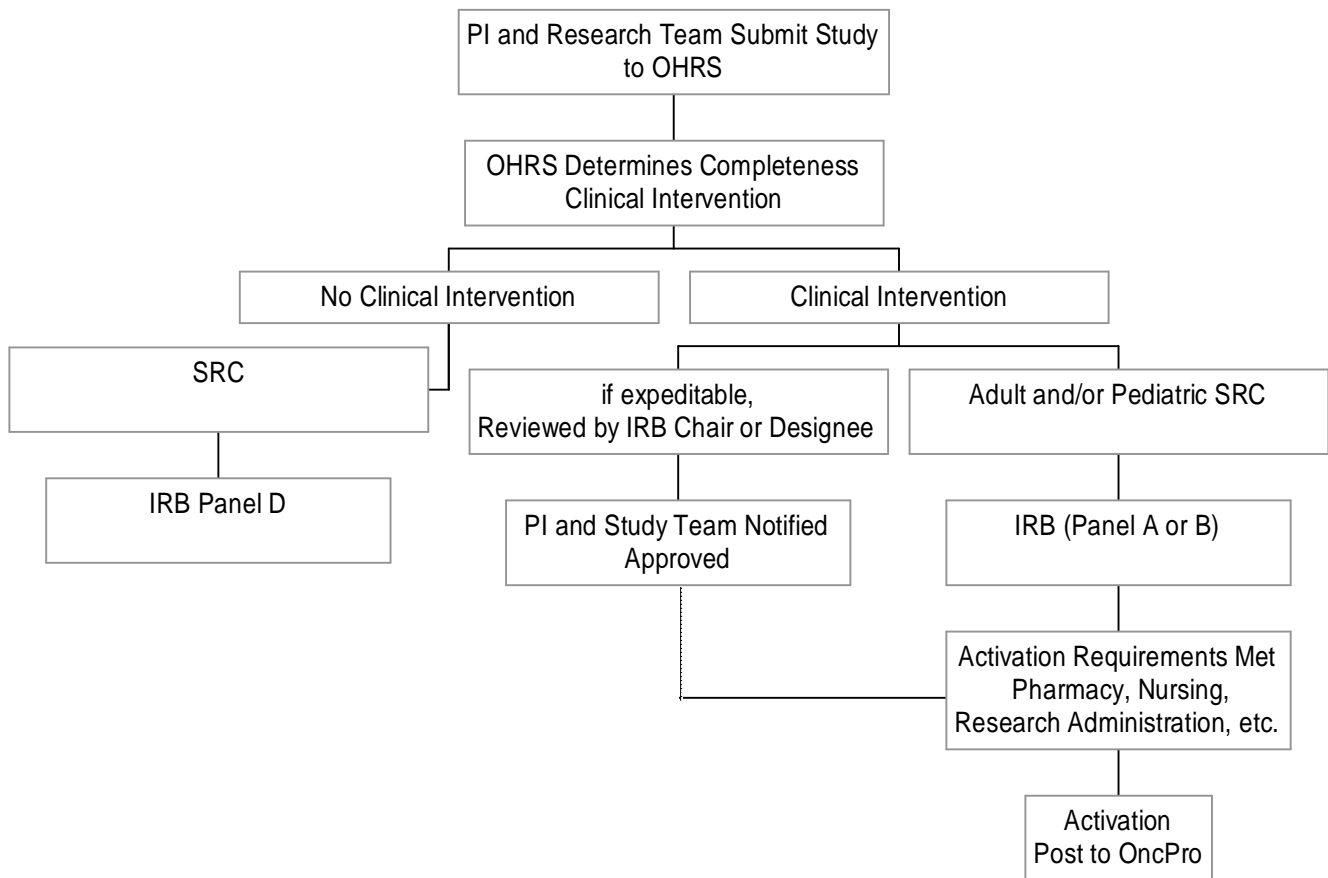
This exemption is for projects conducted by or subject to the approval of federal agencies. In order to meet the criteria for exemption under “public benefit” exemption criteria, the following criteria (see 48 FR 9266-9270) must be satisfied. The research or demonstration project must be conducted pursuant to specific federal statutory authority; there must be no statutory requirement that the project be reviewed by the IRB; the project must not involve significant physical invasions or intrusions upon the privacy of participants. *This category will only be invoked when in the opinion of OHRP it is appropriate.*

- (6) Taste and food quality evaluation and consumer acceptance studies, involving consumption of wholesome foods without additives or consumption of food that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

The following procedures are followed:

1. The investigator will submit the “Request for Exemption or Determination That Activity Is Not Human Subject Research” form, copies of grants, and proposals for funding and all other supporting documents, for review by the Senior Director or Deputy Director of the OHRS.
2. Once exemption has been determined, the investigator will receive an exemption letter explaining why the study meets the criteria for exemption and the related criteria from the regulations will be cited. Studies deemed exempt do not require continuing review. However, any changes to the research which may change the status from exempt to expeditable, for example, must be communicated by the investigator to the IRB via the Senior Director or Deputy Director of the OHRS.

20.12 New Submission Flow Chart



20.13 Protocol Activation and Distribution

After a protocol is approved and all activation requirements have been met, the PI will receive a memo indicating that the trial has been activated. The date of activation is the date when the investigator may begin participant accrual and actually start the trial.

Once a trial has been activated, a full copy of the protocol document, consent form, eligibility checklist, and priority list will be available online via OncPro. Only the online version of the protocol and consent form may be used to ensure that the most updated and accurate information is used.

Although investigators may register their participants through the QACT registration system, all investigators are responsible for maintaining accurate records on the number of participants enrolled in their trials. Enrollment cannot be exceeded without IRB approval.